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(54) **HCV NS3 PROTEASE INHIBITORS**

HCV NS3 PROTEASEINHIBITOREN

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- **INGALLINELLA E A: "Potent peptide inhibitors of human HCV NS3 protease are obtained by optimizing the cleavage products" BIOCHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. EASTON, PA, vol. 37, 23 June 1998 (1998-06-23), pages 8906-8914, XP002086572 ISSN: 0006-2960**

EP 1 230 260 B1

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Description

TECHNICAL FIELD

[0001] This invention relates to compounds which can act as inhibitors of the hepatitis C virus (HCV) NS3 protease, to uses of such compounds and to their preparation.

BACKGROUND ART

[0002] The hepatitis C virus (HCV) is the major causative agent of parenterally-transmitted and sporadic non-A, non-B hepatitis (NANB-H). Some 1% of the human population of the planet is believed to be affected. Infection by the virus can result in chronic hepatitis and cirrhosis of the liver, and may lead to hepatocellular carcinoma. Currently no vaccine nor established therapy exists, although partial success has been achieved in a minority of cases by treatment with recombinant interferon-α, either alone or in combination with ribavirin. There is therefore a pressing need for new and broadly-effective therapeutics.

[0003] Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (N-terminal part of NS3), a helicase (C-terminal part of NS3), and an RNA-dependent RNA polymerase (NS5B). The NS3 protease is located in the N-terminal domain of the NS3 protein, and is considered a prime drug target since it is responsible for an intramolecular cleavage at the NS3/4A site and for downstream intermolecular processing at the NS4A/4B, NS4B/5A and NS5A/5B junctions.

[0004] Previous research has identified classes of peptides, in particular hexapeptides, showing degrees of activity in inhibiting the NS3 protease. The aim of the present invention is to provide further compounds which exhibit similar, and if possible improved, activity.

[0005] According to the nomenclature of Schechter & Berger (1967, Biochem. Biophys. Res. Commun. 27, 157-162) cleavage sites in substrates for the NS3 protease are designated P6-P5-P4-P3-P2-P1...P1'-P2'-P3'-P4'-, with each P representing an amino acid, and the scissile bond lying between P1 and P1'. Corresponding binding sites on the enzyme are indicated as S6-S5-S4-S3-S2-S1...S1'-S2'-S3'-S4'.

[0006] The present applicant has previously disclosed so called product inhibitors which are based on the P-region of the natural cleavage sites and which have been optimised to low nanomolar potency ((1998) Biochemistry 37: 8899-8905 and (1998) Biochemistry 37: 8906-8914. These inhibitors extract much of their binding energy from the C-terminal carboxylate, the remaining interactions with NS3 being similar to the ones used by the natural substrates, including binding in the S_1 pocket and the prominent electrostatic interaction of the P6-P5 acidic couple.

[0007] At variance with the P region, the P' region of the substrate, while being important for catalysis, does not influence significantly ground-state binding to the enzyme as expressed by the Km value. In other words, binding energy released by the substrate interaction with the enzyme to form an initial non-covalent complex is essentially due to the interaction of the residues of the P region; the P'region residues contribute to a lesser extent to the binding energy. Accordingly, peptides based on the P'region of the natural substrates (spanning residues P_1'-P_{10}') do not inhibit NS3 to any significant extent. This notwithstanding, inspection of the crystal structure of NS3 with or without 4A (and more recently of the NMR structure of NS3) shows the presence of binding pockets in the S' region which might be exploited for the binding of active-site directed inhibitors. S'-binding ligands would therefore display a range of interactions with the enzyme different from the ones used by the substrate, and represent a novel class of NS3 inhibitors.

[0008] Landro et al in (1997) Biochemistry 36, 9340-9348 synthesized certain non-cleavable decapeptides based on the NS5A/5B cleavage site by substituting the P_1' serine by a bulky cyclic aromatic (tetrahydroisoquinoline-3-carboxylic acid) or smaller cyclic alkyl compound (proline or pipecolinic acid). They then investigated the interaction of these decapeptides with the substrate binding site of NS3 either in the presence or absence of NS4A cofactor. By looking at the effect of truncation at either the P or P' side of the molecule they concluded that most of the binding energy of the decapeptide is due to interactions with NS3-NS4A complex on the P side of the molecule. Truncation on the P' side produced a relatively large effect in the presence of NS4A cofactor, but less when NS4A was absent. They concluded that the P4' substrate Tyr residue present in their molecules was in close proximity, or in direct contact with NS4A and that this residue contributes significantly to binding in the presence of NS4A.

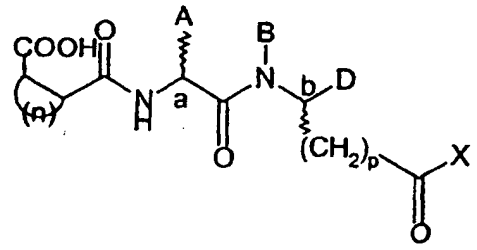
[0009] WO-A-00/31129 describes the development of inhibitors which are more powerful than those described by Landro et al because they have better binding on their P' side. In other words, the inhibitors take advantage of binding to the S' region in addition to binding to the S-region of NS3. By varying the P' amino acid residues, it was shown that the binding energy which may be extracted from S'-region binding is substantial, since inhibitors with optimised and non-optimised P'-regions differ in potency > 1000-fold. Since no activity was present in any of the peptides corresponding to the isolated P'-region, optimisation of an S'-binding fragment was pursued in the context of non-cleavable decapeptides spanning P_6-P_4'.

[0010] Many of the compounds described in WO-A-00/31129 are oligopeptides, some including as many as ten

amino acid residues. Peptidic molecules of this length may be unsuitable for peroral administration because they are subject to degradation in the digestive tract. Thus, it is desirable to develop shorter peptides or molecules having less peptidic character. With this in mind, the present inventors sought to develop a "collected product" inhibitor by combining an optimised P_2'-P_4' fragment with a carboxylate positioned in the same way as the carboxylate in the P-region product inhibitors. They further sought to use the optimised P_2'-P_4' fragment (cyclohexylalanine-aspartic acid-leucine-NH_2) in the design of small molecular weight inhibitors also having a carboxylate appropriately positioned for binding to the enzyme.

SUMMARY OF THE INVENTION

[0011] According to a first aspect of the present invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof:



(I)

[0012] Each of the stereocentres designated "a" and "b" is independently in the R configuration or the S configuration.

[0013] Such compounds are suitable for pharmaceutical use and, in particular as inhibitors of HCV NS3 protease. Thus, embodiments of the compound of the above first aspect may be useful in the manufacture of medicaments for the prevention or treatment of hepatitis C virus infection.

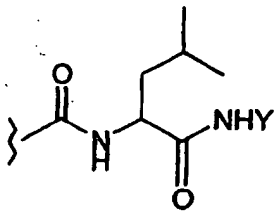
[0014] In formula (I):

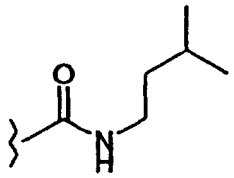
represents a carbocyclic ring and (n) is the total number of carbon atoms in the ring and may be between 4 and 8, but is preferably 5 or 6; the ring may be aromatic or aliphatic;

A is the sidechain of cyclohexylalanine or of an optionally substituted phenylglycine;

B is hydrogen, alkyl of 1-6, preferably 1-2, particularly 1 carbon atom, or is an aralkyl group containing between 7 and 18, preferably from 8 to 14 carbon atoms;

D is hydrogen, or a group of formula:

 ; or less preferably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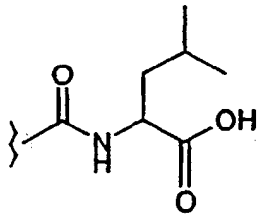


where Y is hydrogen or an alkyl containing 1 to 6 preferably up to 3, especially 2 carbon atoms, or a cycloalkyl group containing 3 to 8 carbon atoms.

p is 1 or 2, preferably 1; and

X is selected from hydroxyl, lower (C_{1-6}) alkoxy groups;

provided that if B is hydrogen or lower alkyl, D is not also hydrogen, and if D is hydrogen B is an aralkyl group.

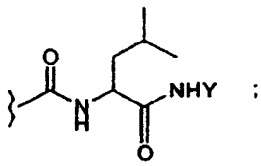
[0015] An embodiment of the first aspect is a compound of formula (I) wherein

represents a benzene ring or a non-aromatic carbocyclic ring and (n) is the total number of carbon atoms in the carbocyclic ring and is from 4 to 8;

A is (i) cyclohexylmethyl- or (ii) phenyl optionally substituted with from 1 to 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, -O-C_{1-4} alkyl, O-C_{1-4} fluoroalkyl, and R^a-C(=O)O-, where R^a is naphthylmethyl-, 2,2-diphenylethyl-, or carboxycyclohexyl-;

B is hydrogen, alkyl of 1-6 carbon atoms or is an aralkyl group containing from 7 to 18 carbon atoms in which the aryl group is optionally substituted with one or more substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, -O-C_{1-4} alkyl, and -O-C_{1-4} fluoroalkyl;

D is hydrogen, or a group of formula: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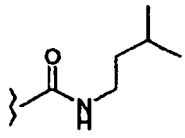
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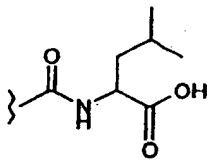


where Y is hydrogen, an alkyl group containing 1 to 6 carbon atoms, or a cycloalkyl group containing 3 to 8 carbon atoms;

each of the stereocentres a and b is independently in the R configuration or the S configuration;

p is 1 or 2; and

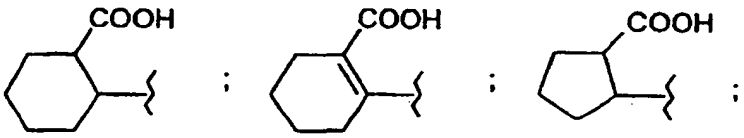
X is selected from hydroxyl, and -O-C_{1-6} alkyl groups;

provided that if B is hydrogen or alkyl, D is not also hydrogen, and if D is hydrogen B is an aralkyl group.

[0016] As used herein the term "halo" implies a halogen atom selected from fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine or bromine. "Alkyl" encompasses both straight and branched chain groups. The term "fluoroalkyl" likewise implies a straight or branched chain alkyl radical which is substituted by one or more fluorine atoms. "Aralkyl" encompasses straight or branched chain alkyl groups substituted with one or more aromatic groups, provided that the total number of carbon atoms lies in the specified range.

DESCRIPTION OF THE INVENTION

[0017] Preferred examples of carbocyclic ring include:



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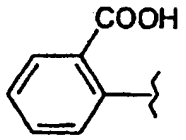
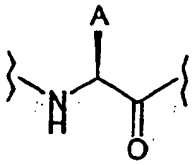


[0018] In the case of the cyclohexyl- and cyclopentyl rings it is highly preferred that the substituents are trans to each other. It is further preferred that the stereochemistry in the carbocyclic ring is 1R,2R.

[0019] The stereochemistry at the group A is preferably as shown below; in other words A is preferably the side chain of an L-amino acid:



[0020] In the case where A is the side chain of phenyl glycine the phenyl ring may be unsubstituted or may be substituted by an optional substituent such as a halogen, preferably fluorine, chlorine or bromine; particularly p-chloro, p-bromo or o-fluoro derivatives, trifluoromethyl (especially p-trifluoromethyl), aralkanoyloxy groups containing from 8 to 20, preferably 12 to 17, especially 12 to 15 carbon atoms and cycloalkanoyloxy groups containing from 5 to 16

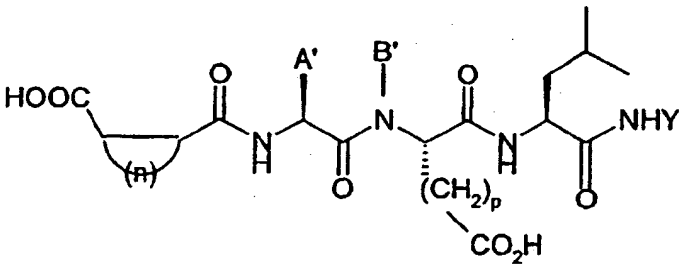
carbon atoms, preferably 7 to 12 carbon atoms.

[0021] It will be apparent that formula (I) includes two subclasses of compound:

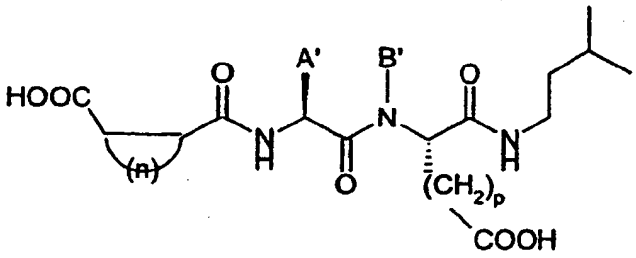
(i) Compounds having B = hydrogen or lower alkyl and in which D is one of the two possible substituents other than hydrogen set out above;
(ii) Compounds having D = hydrogen and in which the group B is an aralkyl group.

[0022] Each of these subclasses is considered in some more detail below.

[0023] Preferred compounds of the first subclass are set out below at formulae (II) and (II'), compounds of formula (II') being less preferred:



(II)



(II')

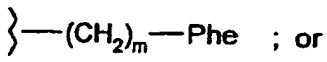
[0024] Although the formulae above show particular, preferred stereochemistry, racemic mixtures and mixtures of diastereomers having the opposite configuration at one or more asymmetric carbon atoms may also be useful.

[0025] In these compounds:

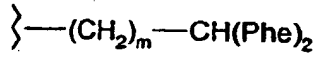
p is 1 or 2, but is preferably 1;
preferred carbocyclic rings are as set out above, with trans 1R,2R cyclohexyl being particularly preferred;
Y is as defined above and is preferably hydrogen, a methyl or ethyl group;
B' is hydrogen or lower alkyl, preferably hydrogen or methyl, especially hydrogen; and
A' is the side chain of cyclohexylalanine, phenylglycine, o-fluorophenylglycine and p-chlorophenylglycine. Stated alternatively, A' is cyclohexylmethyl-, phenyl, o-fluorophenyl or p-chlorophenyl.

[0026] Examples of compounds in this subclass can be found in the tables infra.

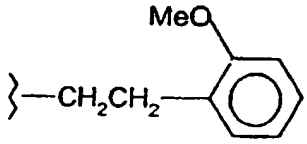
[0027] In the second subclass of compounds, when D is hydrogen, B is an aralkyl group, (e.g. an aralkyl group in which the aryl is optionally substituted with from 1 to 3 substituents independently selected from chloro, fluoro, methyl, CF_3, OCH_3 and OCF_3) especially a group of formula:

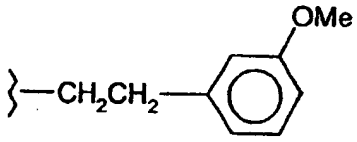


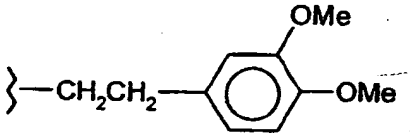
; or

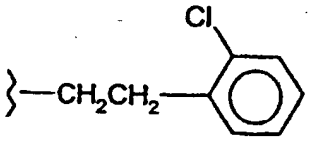


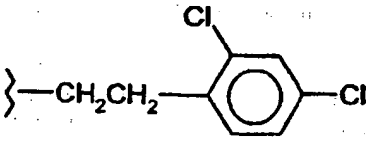
where m is 1 or 2, and Phe is an optionally substituted phenyl group. Suitable optional substituents include halogens, especially chlorine, and lower (C_{1-6}, especially C_1) alkoxy groups. In one embodiment, Phe is phenyl optionally substituted with from 1 to 3 substituents independently selected from chloro, fluoro, methyl, CF_3, OCH_3 and OCF_3. Particularly preferred examples of the B group include:

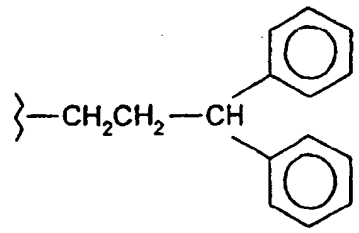




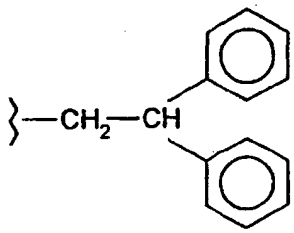




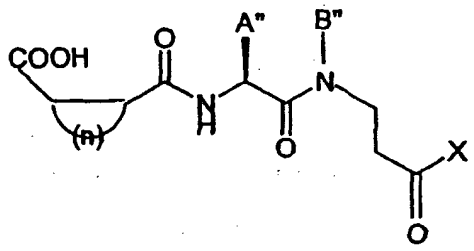




and



[0028] Preferred compounds of this subset include those of formula (III) below:



(III)

[0029] The preferred stereochemistry at A" is shown; however mixtures including the same compound with the reverse stereochemistry here may also be useful.

[0030] Once again, the preferred carbocyclic groups are as set out above with the particularly preferred group being trans 1R,2R cyclohexyl. B" is one of the preferred aralkyl groups listed above and X is preferably OH.

[0031] A" is the side chain of cyclohexylalanine, or of unsubstituted phenylglycine, p-bromophenylglycine, p-trifluoromethylphenylglycine or o-fluorophenylglycine. Stated alternatively A" is cyclohexylmethyl-, phenyl, p-bromophenyl, p-trifluoromethylphenyl, or o-fluorophenyl.

[0032] Preferred compounds of this subclass are set out in the tables B infra.

[0033] Examples of compounds of the present invention may be effective as inhibitors of NS3 protease at micromolar levels. Preferably, the IC_{50}, as measured in the assay described below is less than 100μM, particularly less than 50μM and, optimally, less than 20μM.

[0034] According to a second aspect, the present invention provides a compound, salt or ester according to the first aspect, for use in any therapeutic method, preferably for use in inhibiting the HCV NS3 protease, and/or for use in treating or preventing hepatitis C or a related condition. By "related condition" is meant a condition which is or can be caused, directly or indirectly, by the hepatitis C virus, or with which the HCV is in any way associated.

[0035] According to a third aspect the present invention provides the use of a compound, salt or ester according to the first aspect in the manufacture of a medicament for the treatment or prevention of hepatitis C or a related condition.

[0036] A fourth aspect of the invention provides a pharmaceutical composition which includes one or more compounds, salts or esters according to the first aspect.

[0037] The composition may also include a pharmaceutically acceptable adjuvant such as a carrier, buffer, stabiliser or other excipients. It may additionally include other therapeutically active agents, in particular those of use in treating or preventing hepatitis C or related conditions.

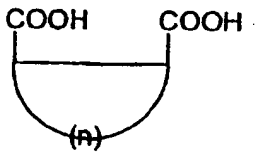
[0038] The pharmaceutical composition may be in any suitable form, depending on the intended method of administration. It may for example be in the form of a tablet, capsule or liquid for oral administration, or of a solution or suspension for administration parenterally.

[0039] According to a fifth aspect of the invention, there is provided a method of inhibiting HCV NS3 protease activity, and/or of treating or preventing hepatitis C or a related condition, the method involving administering to a human or animal (preferably mammalian) subject suffering from the condition a therapeutically or prophylactically effective amount of a composition according to the fourth aspect of the invention, or of a compound, salt or ester according to the first aspect. "Effective amount" means an amount sufficient to cause a benefit to the subject or at least to cause a change in the subject's condition.

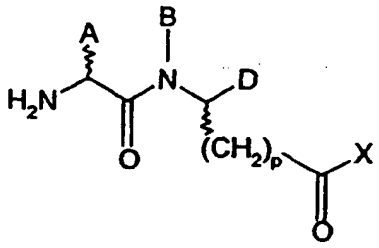
[0040] The dosage rate at which the compound, salt, ester or composition is administered will depend on the nature of the subject, the nature and severity of the condition, the administration method used, etc. Appropriate values can be selected by the trained medical practitioner. Preferred daily doses of the compounds are likely to be of the order of about 1 to 100 mg, say 0.01 to 2 mg/kg. The compound, salt, ester or composition may be administered alone or in combination with other treatments, either simultaneously or sequentially. It may be administered by any suitable route, including orally, intravenously, cutaneously, subcutaneously, etc. It may be administered directly to a suitable site or in a manner in which it targets a particular site, such as a certain type of cell - suitable targeting methods are already known.

[0041] A sixth aspect of the invention provides a method of preparation of a pharmaceutical composition, involving admixing one or more compounds, salts or esters according to the first aspect of the invention with one or more pharmaceutically acceptable adjuvants, and/or with one or more other therapeutically or prophylactically active agents.

[0042] In a seventh aspect of the invention a method is provided for synthesizing the compounds of the first aspect. In general, a diacid of formula:



or an activated form thereof, such as the acid anhydride, is condensed with a suitably protected molecule of formula:



where n, A, B, D, p and X are as defined above. Suitable protecting groups will be apparent to the person of skill in the art and are chosen with a view to preventing reaction of any reactive groups in the groups A, B, D and X with the (activated) diacid or with the NH_2 group.

[0043] In the case of the first subclass of molecules the peptidic fragment may be synthesized by conventional peptide synthesis using protecting groups well known to peptide chemists. Suitable synthetic procedures include those described in:

[0044] "Fmoc Solid Phase Peptide Synthesis, A Practical Approach", W.C. Chan and P.D. White (Eds), Oxford University Press, Oxford (2000); J. Am. Chem. Soc. 114 (1992) 10646-10647 (Zuckerman, R.N. et al); and Tetrahedron

Lett., 37 (1996) 5277-5280 (Kolodziej S.A. et al).

[0045] Examples of the synthesis of compounds of each subclass are described below. Routine modification of the reaction schemes described could be used to produce other examples of compounds of the invention.

MODES FOR CARRYING OUT THE INVENTION

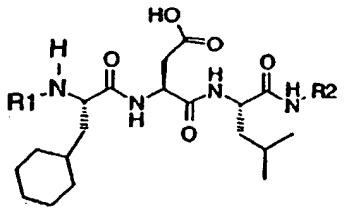
EXAMPLES

[0046] Embodiments of the compounds of the present invention are described below by way of example only.

[0047] The following tables I to IV set out exemplary compounds of the invention, together with IC_{50} values for inhibition of HCV NS3 protease as measured by the microplate protease activity assay described subsequently. The configuration of each asymmetric carbon in the exemplified compounds is indicated in the right hand column of each table.

[0048] Examples of the synthesis of some of the compounds included in the tables follows the tables.

Table I



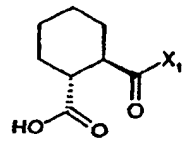
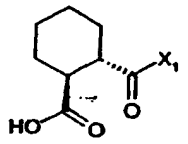
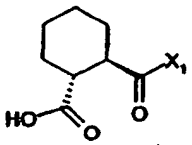
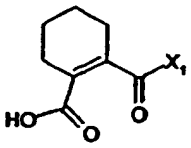
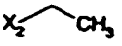
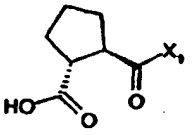
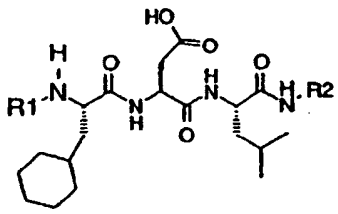
Ex. No.	R1	R2	IC 50	Chiral centres
1			15uM	R,R,S,S,S
2			54uM	S,S,S,S,S
3			32 uM	R,R,S,S,S
4			38 uM	S,S,S
5			60 uM	R,R,S,S,S

Table I



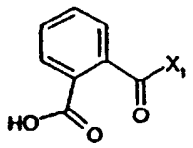
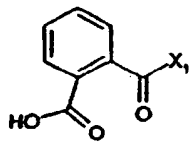
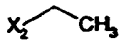
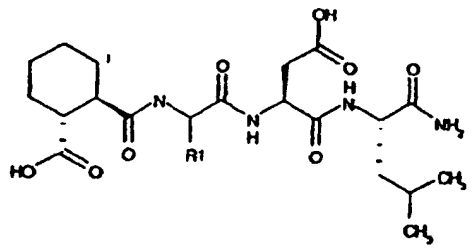
Ex. No.	R1	R2	IC 50	Chiral centres
6			64 uM	S,S,S
7			64 uM	S,S,S

Table II



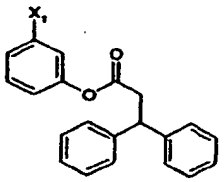
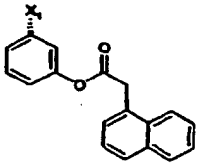
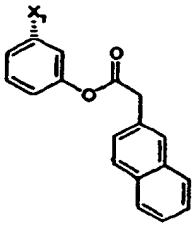
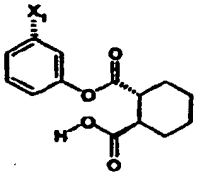
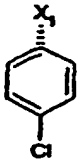
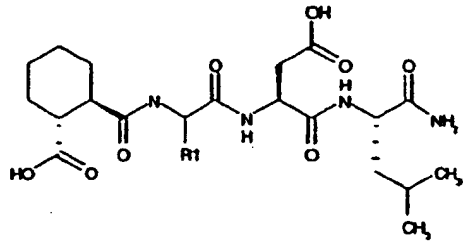
Ex. No.	R1	IC 50	Chiral centres
8	one isomer 	13 uM	R,R,[R/S*],S,S *single isomer, not identified
9		22 uM	R,R,S,S,S
10		22 uM	R,R,S,S,S
11		35 uM	R,R,S,(R,R),S,S
12		37uM	R,R,S,S,S

Table II



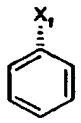
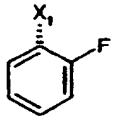
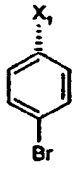
Ex. No.	R1	IC 50	Chiral centres
13		40uM	R,R,S,S,S
14		47uM	R,R,S,S,S
15		26uM	R,R,S,S,S

Table III

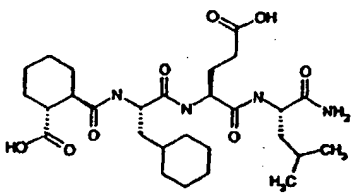
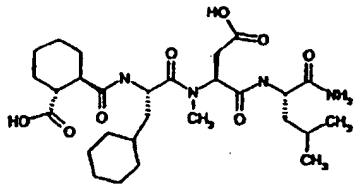
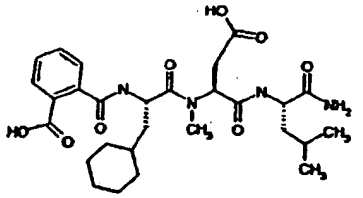
Ex. No.		IC 50	Chiral centres
16		41uM	R,R,S,S,S
17		100 uM	R,R,S,S,S
18		115 uM	S,S,S

Table IV

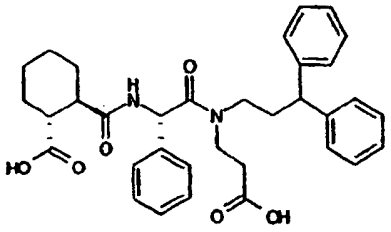
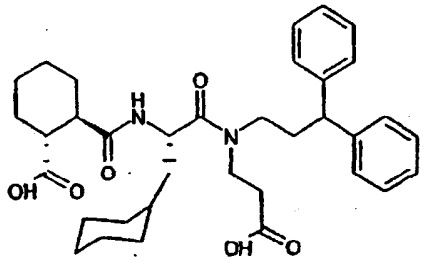
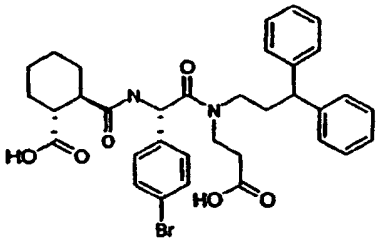
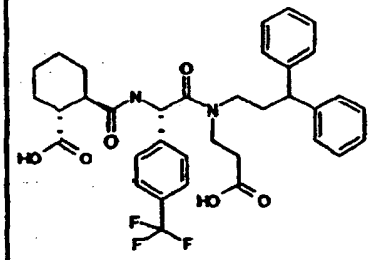
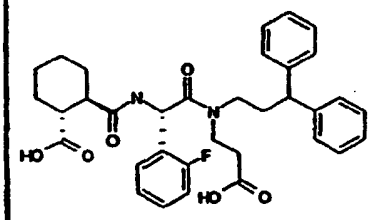
Ex. No.		IC 50	Chiral centres
19		14uM	R,R,S
20		55 uM	R,R,S
21		1.7 uM	R,R,S
22		7uM	R,R,S
23		6uM	R,R,S

Table IV

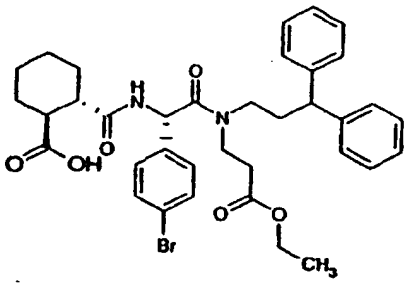
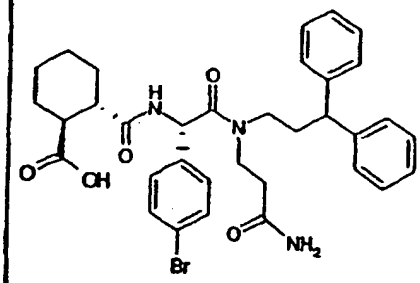
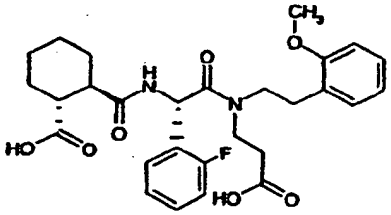
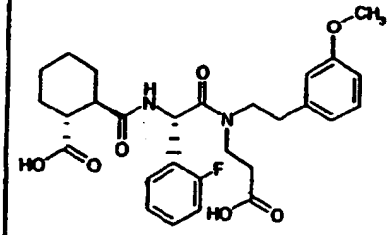
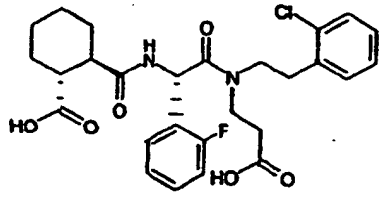
Ex. No.		IC 50	Chiral centres
24		60µM	R,R,S
25		59µM	R,R,S
26		44uM	R,R,S
27		66uM	R,R,S
28		70uM	R,R,S

Table IV

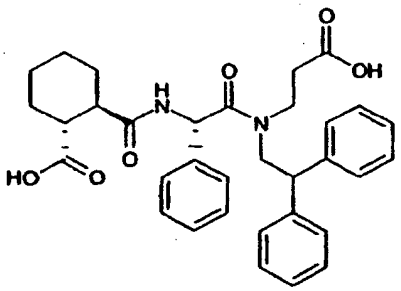
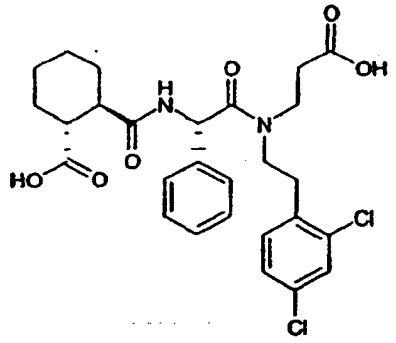
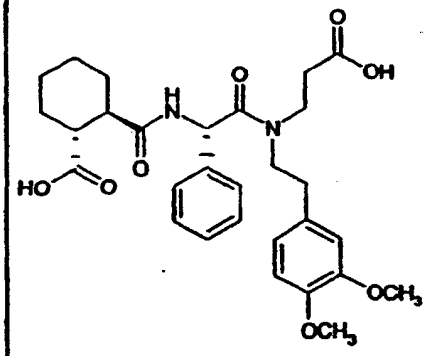
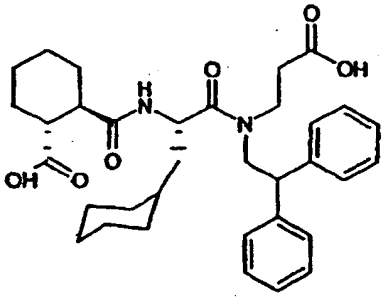
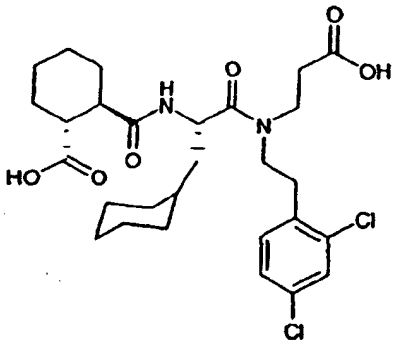
Ex. No.		IC 50	Chiral centres
29		39 uM	R,R,S
30		49uM	R,R,S
31		123 uM	R,R,S
32		133 uM	R,R,S

Table IV

Ex. No.		IC 50	Chiral centres
33		177 uM	R,R,S

SYNTHETIC EXAMPLES

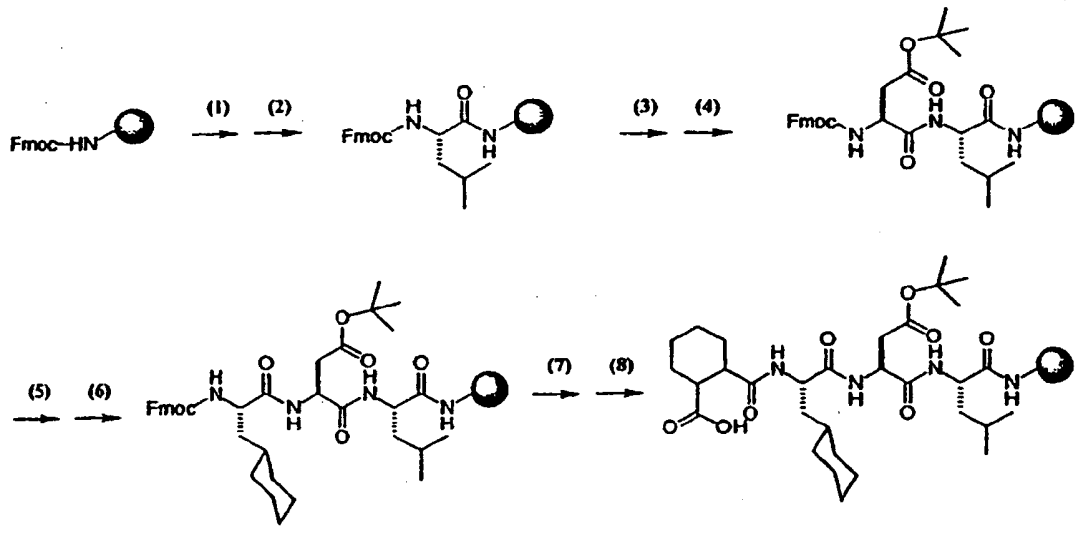
General methods.

[0049] Unless indicated otherwise, all the materials were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed in silica gel 60 F_{254} precoated plates (Merck). Analytical HPLC was performed on a Beckman System Gold chromatograph equipped with a diode-array detector (dual wavelength monitoring, 214 and 254 nm) and a Beckmann C-18 column (250 x 4.6 mm, 5 µm), operating flow rate 1 mL min^{-1}. Preparative HPLC was performed on a Waters 600E chromatograph equipped with a Jasco UV-975 detector (monitoring wavelength, 254 nm and 214 nm), Waters Delta-Pak™ C-18 column (100 x 250 mm, 15 µm). The operating flow rate was 30 mL min^{-1}. The solvent system was: eluent A, water (0.1% TFA); eluent B, MeCN (0.1% TFA). NMR spectra were recorded on a Brucker instrument operating at 400 MHz (^{1}H). Chemical shifts are reported in ppm relative to the solvent residual signal. Unless indicated otherwise, the amino acids in the examples below are always in the L-configuration.

EXAMPLE A:

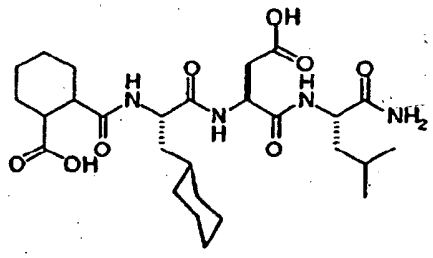
Synthesis of R,R-cyclohexane-1,2-dicarboxylate monoamide of Cha-Asp-Leu-NH_2 (Tab. I ex. No 1) and SS-cyclohexane-1,2-dicarboxylate monoamide of Cha-Asp-Leu-NH_2 (Tab. I ex. No 2).

[0050] *Trans*-D,L-cyclohexane-1,2-dicarboxylate monoamide of Cha-Asp-Leu-NH_2 was prepared according to Scheme 1. Manual Solid phase peptide synthesis was performed on 200mg of NovaSyn TGR® resin (0.24mmol/g, 0.048mmol) using a 5-fold excess (over the resin amino groups) of amino acid/ PyBOP/HOBt/DIEA (5:5:5:10), or 5-fold excess of *trans*-1,2-cyclohexanedicarboxylic anhydride.



[0051] Scheme 1. (1), (3), (5) and (7): 1.5ml of 20% piperidine/DMF, 20 min, 25°C, followed by DMF washes (5 x 2 ml); (2): 85mg of Fmoc-Leu-OH (0.24mmol), 125mg of PyBOP (0.24mmol), 37mg of HOBt (0.24mmol) and 82µl of DIEA (0.48mmol) dissolved in 200µl of DMF. Coupling time: 30 min, followed by DMF washes (5 x 2 ml); (4): as in (2), but 99mg of Fmoc-Asp(OtBu)-OH (0.24mmol) instead of Fmoc-Leu-OH; (6): as in (2), but 94mg of Fmoc-Cha-OH (0.24mmol) instead of Fmoc-Leu-OH; (8): 37mg of *trans*-1,2-cyclohexanedicarboxylic anhydride (0.24mmol) dissolved in 200µl of DMF. Coupling time: 30 min, followed by DMF washes (5 x 2 ml).

[0052] At the end of the assembly, the resin was washed with DMF, Methanol, and DCM and dried to constant weight *in vacuo*. The compound was simultaneously cleaved from the resin and side-chain deprotected by treatment of the dry resin with 1.5ml of TFA/H_2O 90/10 for 1h. The TFA solution was filtered from the resin and concentrated *in vacuo*. 1.5 ml of cold diethylether was added (bringing about visible precipitation) and the solvent was evaporated; this operation was repeated twice. After a last addition of cold diethylether, the suspension was centrifuged, the ether removed and the solid dried *in vacuo* The compound



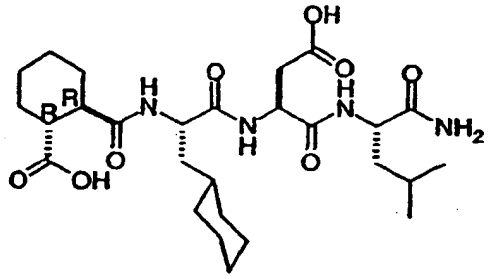
was obtained as a mixture of two diastereoisomers. Yield: 15mg (56.6%).

[0053] Analytical HPLC of the product was performed using isocratic elution at 30%B for 5 min, followed by a linear gradient 30%-70%B over 20 min. The two peaks eluted at t_R= 13.7' and t_R= 19.0' corresponded to the expected diastereoisomers. Preparative HPLC was performed as follows: the crude sample (15mg) was dissolved in 0.5ml of DMSO, diluted to 7 ml with H_2O/CH_3CN, and loaded onto the preparative column at a flow rate of 5 ml/min. The flow was then raised to 30 ml/min and the preparative run started with an isocratic step (30%B, 5 min) followed by a linear gradient 30%-60%B over 20 min. The first eluted species was named "isomer A" while the second one was named "isomer B". Both were lyophilized. Isomer A (Tab. I Ex. No 1). Analytical HPLC: linear gradient 35%-65%B over 20 min, t_R=7.64', purity > 99%; Isomer B (Tab. I ex. No 2): Analytical HPLC: linear gradient 35%-65%B over 20 min, t_R=13.05', purity > 99%;

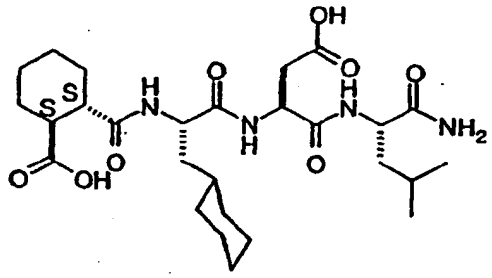
[0054] The other analytical data were identical for the two isomers. Ion-spray mass spectrometry: molecular weight = 552.5 Da (expected M.W. 552.67 Da). ^{1}HNMR (400.13MHz, DMSO, 300K): δ 8.00 (d, 1H), 7.93 (d, 1H), 7.65 (d, 1H), 7.05 (d, 2H), 4.45 (multiplet, 1H), 4.16 (multiplet, 2H), 2.72-2.68 (dd, 1H), 2.57 (d, 1H), 2.45-2.35 (broad multiplet, 2H), 1.95-1.84 (broad multiplet, 2H), 1.76-1.00 (series of multiplets, 22H), 0.87 (d, 3H), 0.77 (d, 3H).

Assignment of the absolute configuration of Isomers A and B.

[0055] In order to assign the absolute configuration of the two chiral carbons at the trans-carboxycyclohexanecarbonyl moiety of the two diastereoisomers (Tab. I ex. No 1 and No 2), the synthesis was repeated using the (1R,2R)-cyclohexanedicarboxylic acid to obtain the corresponding isomer in the final product. The synthetic scheme was as previously described (Scheme 1) with the exception of step (8):
41mg of (1R,2R)-cyclohexanedicarboxylic acid (0.24mmol), 125mg of PyBOP (0.24mmol), 37mg of HOBt (0.24mmol) and 82µl of DIEA (0.48mmol) dissolved in 200µl of DMF. Coupling time: 30 min, followed by DMF washes (5 x 2 ml). The work-up and cleavage were also performed as previously described. Analytical HPLC of the crude product in the same conditions used for the diastereoisomeric mixture showed a single peak with a t_R= 7.62' corresponding to the retention time of the isomer A (Tab. I ex. No 1). Co-injection with purified isomer A revealed a single peak with t_R= 7.59'. Therefore the assignment of the stereochemistry for the previously synthesized isomers A and B was:



Isomer A

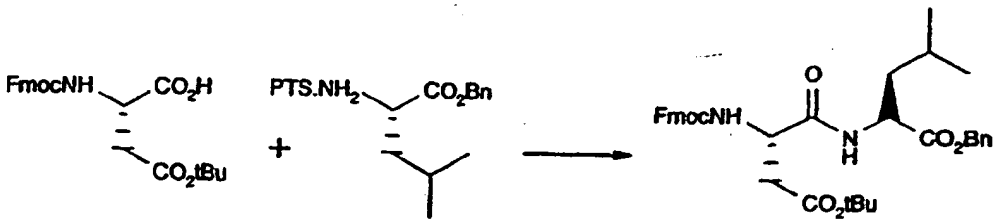


Isomer B

EXAMPLE B: Synthesis of *Trans*-D,L-cyclohexane-1,2-dicarboxylate monoamide of Cha-Asp-Leu-NHEt ; R,R-cyclohexane-1,2-dicarboxylate monoamide of Cha-Asp-Leu-NHEt ; and S,S-cyclohexane-1,2-dicarboxylate monoamide of Cha-Asp-Leu-NHEt (Tab. I ex. No 3).

Step 1 : Synthesis of Fmoc-Asp-(OtBu)-Leu-OBn.

[0056]

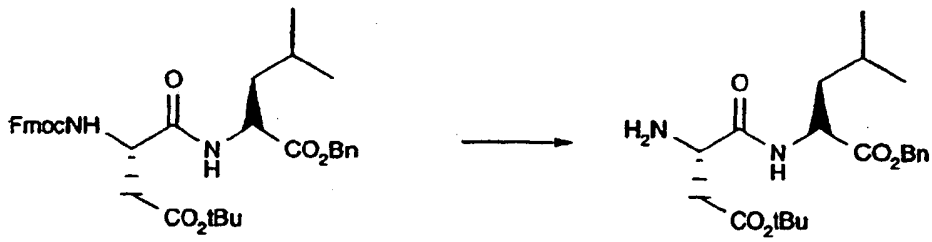


[0057] Fmoc-Asp(OtBu)-OH (5.00 gr, 12.15 mmol) was dissolved in 200 mL DCM. EDCA (2.33 gr, 12.15 mmol), HOBT (6.32 gr, 12.15 mmol), H-Leu-OBn PTS salt (4.78 gr, 12.15 mmol) and DIPEA (2.11 mL, 12.15 mmol) were added in the order while stirring.

[0058] After 12 hrs the solution was washed with 1N HCl (3 x 100 mL), 5% Na_2CO_3 (3 x 100 mL) and brine, then dried (Na_2SO_4) and concentrated to yield 7.60 gr of a white foam (98%).
^{1}H-NMR ($CDCl_3$) δ 7.80(d, 2H), 7.60(d, 1H), 7.50-7.30(m, 10H), 7.00(d, NH), 6.00(d, NH), 5.20(m, 2H), 4.62(m, 2H), 4.41(d, 2H), 4.24(dd, 1H), 2.93(dd, 1H), 2.58(dd, 1H), 1.70-1.55(m, 3H), 1.45(s, 9H), 0.93(s, 9H).

Step 2 : synthesis of H-Asp(OtBu)-LeuOBn.

[0059]

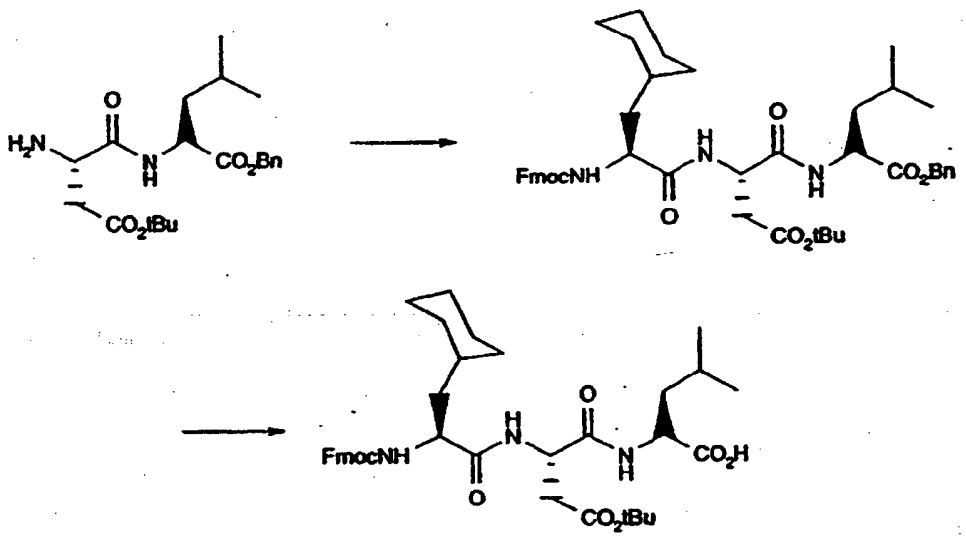


[0060] Fmoc-Asp(OtBu)-Leu-OBn (1.00 gr, 1.60 mmol) was dissolved in 25 mL DCM. 4-aminomethylpiperidine (1 mL, 8.0 mmol) was added and stirring was continued at room temperature. At the end of the reaction (TLC control, silica, EtOAc/dichloromethane 1:4) the solution was washed with water (3 x 5 mL) and brine, dried over Na_2SO_4 and filtered. The resulting solution was directly poured onto a chromatographic column previously equilibrated with DCM. Chromatographic purification (eluent DCM, then dichloromethane/EtOAc 4:1) yielded 606 mg of product (97%) as a colourless oil.

^{1}H-NMR ($CDCl_3$) δ 7.71(d, 1H), 7.35(m, 5H), 5.10(m, 10H), 7.00(d, NH), 6.00(d, NH), 5.20(m, 2H), 4.62(m, 2H), 4.41 (d, 2H), 4.24(s, 2H), 4.60(m, 1H), 3.65(dd, 1H), 2.80(dd, 1H), 1.70-1.50(m, 3H), 1.40(s, 9H), 0.90(m, 6H).

Step 3 : Synthesis of Fmoc-Cha-Asp(OtBu)-Leu-OBn.

[0061]



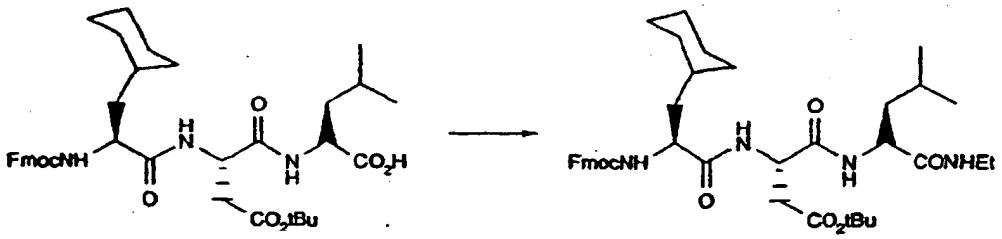
[0062] H-Asp(OtBu)-Leu-OBn (606 mg, 1.54 mmol) was dissolved in DCM (10 mL) and Fmoc-Cha-OH (610 mg, 1.54 mmol), EDCA (330 mg, 1.69 mmol) and HOBT (1.2 gr, 2.31 mmol) were added. The resulting mixture was stirred at room temperature for 12 h. The solution was diluted with EtOAc (150 mL) , washed with 1N HCl (3 x 100 mL), 5% Na_2CO_3 (3 x 50 mL) and brine then dried (Na_2SO_4) and concentrated to obtain 1.10 gr of a white solid (99%), which was used without further purification in the next step. Fmoc-Cha-Asp(OtBu)-Leu-OBn (1.10 gr, 1.54 mmol) was dissolved in MeOH (10 mL), 50 mg of 5% Pd/C were added and the resulting misture was stirred for 6 h under H_2 atmosphere. After filtration and distillation of the solvents *in vacuo*, 803 mg of a white foam were obtained (77%).

^{1}H-NMR ($CDCl_3$) δ 7.80 (d, 2H), 7.60(m, 2H), 5.10(m, 10H), 7.42(m, 3H), 7.31(m, 2H), 7.20(d, 1H), 5.20(d, 1H), 4.80

(m, 1H), 4.40-4.34(m, 3H), 4.21(m, 2), 2.90(dd, 1H), 2.60(dd, 1H), 1.84-1.350(m, 14H), 1.40(s, 9H), 0.90(m, 6H).

Step 4 : Synthesis of Fmoc-Cha-Asp(OtBu)-Leu-NHEt.

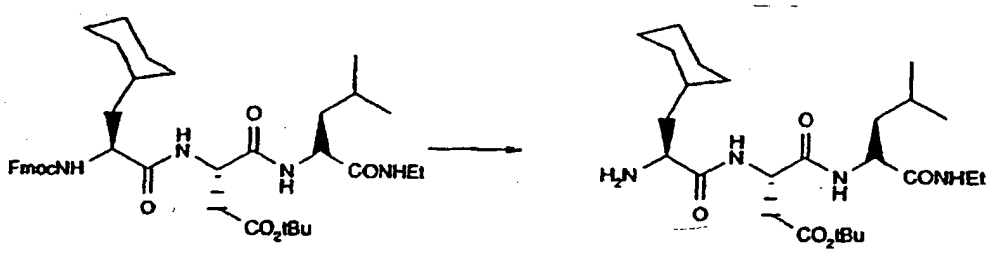
[0063]



[0064] A solution of Fmoc-Cha-Asp(OtBu)-LeuOH (803 mg, 1.19 mmol), EDCA (341 mg, 1.77 mmol) and HOBT (115 mg, 1.77 mmol) in DCM (20 mL) was stirred at room temperature. A solution of ethylamine hydrochloride (145 mg, 1.77 mmol) and DIPEA (0.31 mL, 1.77 mmol) in DCM (20 mL) was added dropwise. After 5 h the solution was diluted with 50 mL DCM, washed with 1N HCl (3 x 25 mL), 5% Na_2CO_3 (3 x 50 mL) and brine, then dried (Na_2SO_4)and concentrated to yield 1.00 g of a white solid which was used without further purification in the next step.
^{1}H-NMR ($CDCl_3$) δ 7.80(d, 1H), 7.60(m, 3H), 7.4-(m, 2H), 7.31(m, 2H), 7.00(d, 1H), 6.55(dd, 1H), 5.20(d, 1H), 4.60(m, 1H), 4.50-4.40(m, 3H), 4.30(m, 1H), 4.40(m, 1H), 3.30(m, 2H), 2.90(dd, 1H), 2.35(dd, 1H), 1.80-1.20(m, 12H), 1.35(s, 9H), 1.13(t, 3H), 0.90(m, 4H), 0.80(m, 6H).

Step 5 : synthesis of H-Cha-Asp(OtBu)-Leu-NHEt.

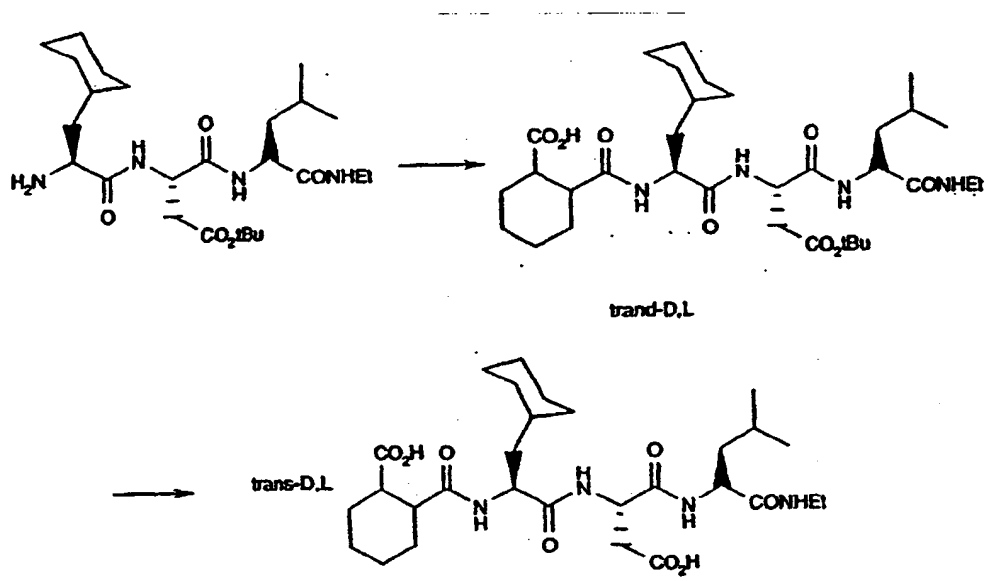
[0065]



[0066] Fmoc-Cha-Asp(OtBu)-Leu-NHEt (1.06 gr, 1.19 mmol) was dissolved in 10 mL DCM. 4-aminomethylpiperidine (1 mL, 8.0 mmol) was added and stirring was continued at room temperature. At the end of the reaction (TLC control, silica, EtOAc/DCM 1:4) the solution was washed with water (3 x 5 mL) and brine, dried over Na_2SO_4 and filtered. The resulting solution was directly poured on a chromatographic column previously equilibrated with DCM. Chromatographic purification (eluent DCM, then DCM/EtOAc 4:1) yielded 308 mg of product (55%).
^{1}H-NMR ($CDCl_3$) δ 8.20(d, 1H), 6.60(d, 1H), 6.45(dm, 1H), 4.68(m, 1H), 4.40(m, 1H), 3.44(dd, 1H), 3.26(m, 2H), 2.80 (m, 2H), 1.40-1.16(m, 14H), 1.45(s, 9H), 1.13(t, 3H), 1.00(m, 2H), 0.9(m, 6H).

Step 6 : Synthesis of Trans-D,L-cyclohexane-1,2-dicarboxylate monoamide of Cha-Asp-Leu-NHEt.

[0067]



[0068] A solution of H-Cha-Asp(OtBu-Leu-NHEt (100 mg, 0.21 mmol), DMAP (cat. amount) and trans-(D,L)-cyclohexanedicarboxylic anhydride in DCM (5 mL) was stirred at room temperature for 3 h. Then the solution was diluted with DCM (20 mL), washed with 1N HCl (2 x 10 mL) and brine, then dried and concentrated to obtain 98 mg (73%) of a white solid.

The solid was dissolved in water (1 mL) and TFA (4 mL) and was stirred at room temperature for 1 h. Solvents were then distilled off *in vacuo*. Trituration of the residual oil with diethyl ether yielded 60 mg of a white solid.

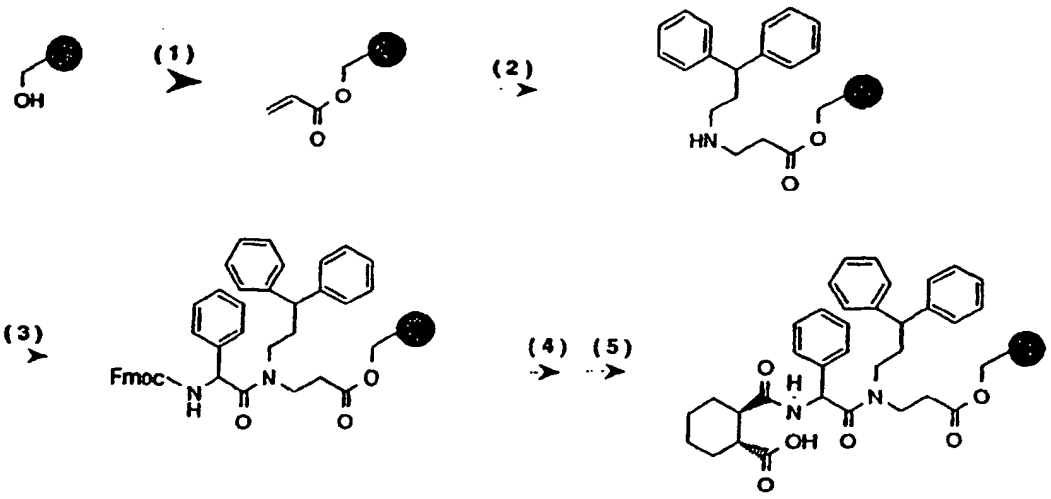
^{1}H-NMR (DMSO-^{6}d) δ 8.20, 8.00, 7.90, 7.85, 7.65, 7.60, 7.50 (NHs, 4H), 4.45(m, 1H), 4.14(m, 2H), 3.00(dd, 2H), 2.70 (m, 1H), 2.50(m, 1H), 2.41(m, 2H), 2.05-1.05(m, 22H), 1.00(t, 3H), 0.80(dd, 6H), 0.80(m, 2H).

The two distereoisomers were separated by preparative HPLC (linear gradient 30%-90% B in 25 min) to obtain:

R,R-cyclohexane-1,2-dicarboxylate monoamide of
Cha-Asp-Leu-NHEt retention time 10min.
S,S-cyclohexane-1,2-dicarboxylate monoamide of Cha-Asp-Leu-NHEt (Tab. I, **Example No 3**): retention time 20 min.

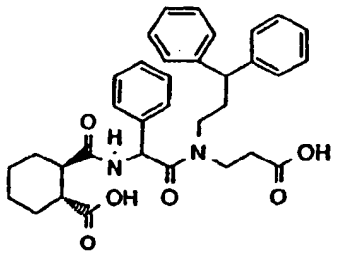
EXAMPLE C: Synthesis of compound (Tab. IV Ex. No 19) and its stereoisomer

[0069] Solid phase synthesis was performed on 100mg of Wang resin (Novabiochem, 0.96mmol/g, 0.096mmol). The compound was prepared according to the following scheme:



[0070] Scheme 2.: **(1):** 76.4µl TEA (0.53mmol), then 38.2 µl ACC (0.48mmol), were added to the resin pre-swollen in 600 µl of DCM. Reaction time: 2h, followed by DCM washes (5 x 2ml). The procedure was repeated with a lower excess of reagents: 46ul of TEA (0.32mmol), then 23 µl of ACC (0.29mmol), were added to the resin swollen in 600 µl of DCM. Reaction time: 2h. The resin was sequentially washed with DCM, DMF and MeOH. **(2):** 184 µl of 3,3-diphenylpropylamine (0.96mmol) dissolved in 776 µl DMSO (1M solution). Reaction time: 22h, room temperature, with stirring. The resin was washed with DMSO, MeOH and DCM. **(3):** 143mg Fmoc-Phg-OH (0.38mmol), 146mg HATU (0.38mmol) and 131 µl DIEA (0.38mmol) dissolved in 400 µl of DMF. Coupling time: 2h, followed by DMF washes (5 x 2ml). Partial racemization of the Phg occurs in these conditions. **(4):** 1.5ml of 20% piperidine/DMF, 20 min, followed by DMF washes (5 x 2ml). **(5):** 81mg of (1R,2R)-cyclohexanedicarboxylic acid (0.48mmol), 250mg PyBOP (0.48mmol), 71mg HOBt (0.48mmol) and 164µl DIEA (0.96mmol) dissolved in 400µl DMF. Coupling time: 1h, followed by DMF washes (5 x 2 ml).

[0071] At the end of assembly, the resin was washed with DMF, MeOH, and DCM and dried to constant weight *in vacuo*. The compound was cleaved from the resin by treatment with 3ml of TFA/H_2O 95/5 for 20 min. The TFA solution was filtered from the resin which was washed with DCM (3 x 1ml). The TFA/DCM solution was concentrated *in vacuo*. 3ml of cold diethylether were added (inducing formation of a fine precipitate) and the solvent evaporated; this operation was repeated once again, then the sample was lyophilized. The compound was obtained as a mixture of diastereoisomers (yield, 39 mg, 71%):



[0072] Analytical HPLC of the product was performed using a linear gradient 30%-80%B over 15 min. The two peaks eluting at t_R= 12.5' and t_R= 14.0' corresponded to the two expected diastereoisomers. Preparative HPLC was performed as follows: the crude sample (10mg) was dissolved in 1ml of DMSO, diluted to 5 ml with H_2O/CH_3CN, and loaded onto the preparative column at a flow rate of 5 ml/min. The flow was then raised to 30 ml/min and the preparative run started with an isocratic step (40%B, 5 min) followed by a linear gradient 40%-80%B over 20 min. The first eluted species was named "isomer A" while the second one was named "isomer B". Both were lyophilized.

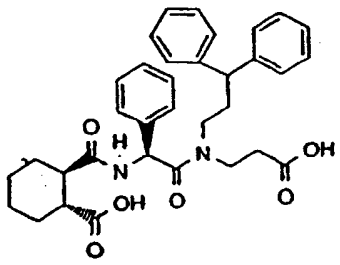
[0073] Isomer A (Tab. IV Ex. No 19). Analytical HPLC: linear gradient 30%-80%B over 15 min, t_R=12.59', purity > 99%;

[0074] Isomer B: Analytical HPLC: linear gradient 30%-80%B over 15 min, t_R=14.08', purity > 99%;

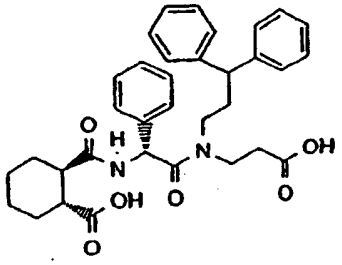
[0075] The other analytical data were identical for both compounds. Ion-spray mass spectrometry: molecular weight

= 570.5 Da (expected M.W. 570.69 Da). ^{1}HNMR (400.13MHz, DMSO, 300K): δ 8.45-8.15 (dd, 1H), 7.43-7.10 (m, 15H), 6.93-6.83 (m, 1H), 5.80-5.40 (dm, 1H), 4.05-2.95 (series of multiplet, 6H), 2.43-2.10 (series of multiplet, 4H), 2.00-1.82 (broad m, 2H), 1.78-1.60 (broad m, 2H), 1.32-1.10 (broad m, 4H).

[0076] By analogy with the previously synthesized analogous compounds, in which the R configuration corresponded to the species with the lower retention time, the S configuration at the Phg was tentatively assigned to isomer A, and the R configuration to isomer B:



Isomer A

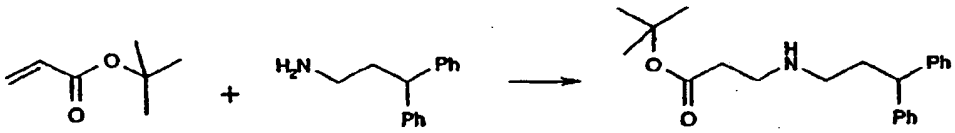


Isomer B

EXAMPLE D: Synthesis of compound (Tab. IV Ex. No 21) and its stereoisomer

Step 1 : Synthesis of N-3,3-diphenylpropyl-β-alanine-OtBu.

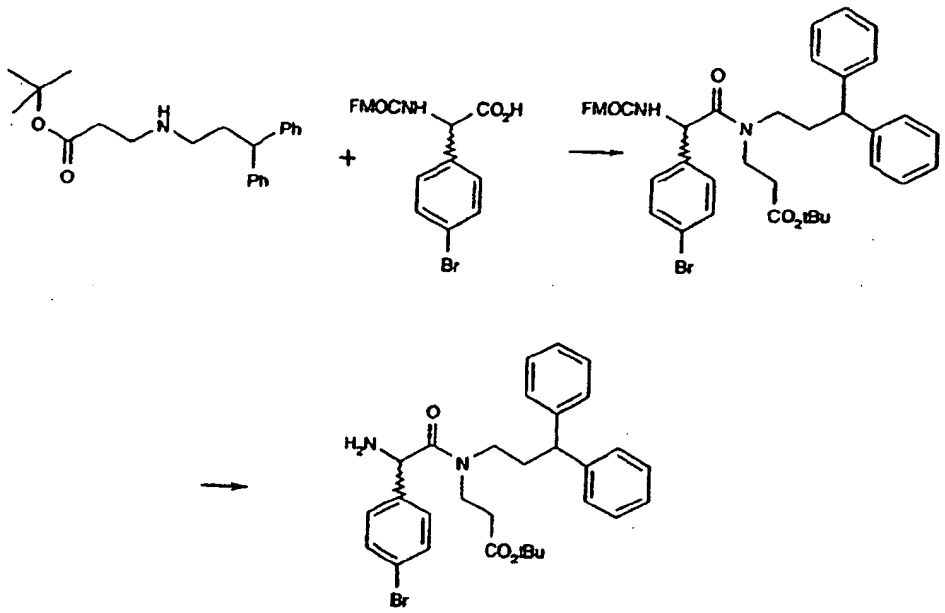
[0077]



[0078] 3,3-diphenylpropylamine (2.00 gr, 9.76 mol) and t-butylacrylate (1.28 gr, 9.76 mmol) in EtOH (5 mL) were stirred at room temperature for 12 h; the solvents were then distilled off *in vacuo*. Chromatographic purification of the residue (silica, DCM/EtOAc 1:1 then DCM/EtOAc 1:1, 1% TEA) yielded 2.61 gr of product (79%) as a colourless oil. ^{1}H-NMR (DMSO-^{6}d) δ 7.25(m, 10H), 2.6(m, 1H), 6.45(dm, 1H), 4.68(m, 1H), 4.40(m, 1H), 3.44(dd, 1H), 3.26(m, 2H), 2.80(m, 2H), 2.3(m, 2H), 2.20(m, 2H), 2.05(m, 2H), 1.30(s, 9H).

Step 2 : Synthesis of 4-bromo-D,L-phenyl glycine ester of N-3,3-diphenylpropyl-β-alanine-OtBu.

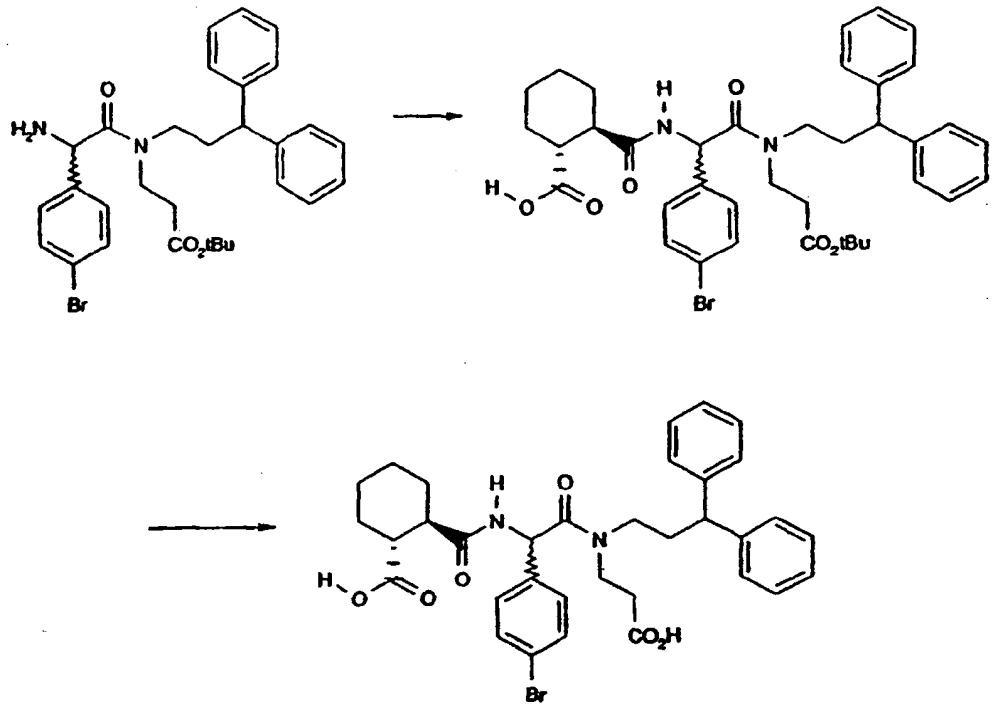
[0079]



[0080]. Fmoc-4-bromo-D,L-phenylglycine (161 mg, 0.36 mmol) was dissolved in 10 mL (1:1) DCM/DMF. HATU (163 mg, 0.43 mmol), DIPEA (0.14 mL, 0.78 mmol) and N-3,3-diphenylpropyl-β-alanine-OtBu (133 mg, 0.39 mmol) were added in that order. Stirring was continued at room temperature for 12 h. The mixture was then diluted with DCM (30 mL), washed with 1N HCl (3 x 10 mL), 10% Na_2CO_3 (2 x 10 mL) and brine, then dried (Na_2SO_4) and concentrated *in vacuo* to yield 314 mg of product as a yellow oil. This was used in the next step without further purification. The oil was dissolved in 15 mL DCM and 0.45 mL of 4-aminomethylpiperidine (3.57mmol) were added. At the end of the reaction (TLC control, DCM/MeOH 9:1) the solution was diluted with 30 mL DCM, washed with water (2 x 10 mL) and brine, dried over Na_2SO_4 and filtered. The resulting solution was directly poured onto a chromatographic column previously equilibrated with DCM. Chromatographic purification (eluent DCM, then DCM/MeOH 9:1) yielded 101 mg of a colourless oil (combined yield for the two steps, 51 %).

Step 3 : Synthesis of R,R-cyclohexane dicarboxylic acid monoamide of (D,L)-p-Br-phenylglycinamide of N-3,3-diphenylpropyl-N-2-carboxyethylamide.

[0081]



[0082] A solution of 4-bromo-D,L-phenyl glycine ester of N-3,3-diphenylpropyl-b-alanine-OtBu (101 mg, 0.18 mmol), R,R-cyclohexanedicarboxylic acid (33 mg, 0.19 mmol), EDCA (35 mg, 0.18 mmol) and DMAP (22 mg, 0.18 mmol) in 5 mL DCM was stirred at room temperature for 12 h. Then it was diluted with DCM (10 mL), washed with 1 N HCl (3 x 5 mL) and brine, dried and concentrated to yield 135 mg of product as a white foam. The foam was dissolved in 10 mL (95:5) TFA/H_2O and stirred for 1 h at room temperature. The solvents were then distilled off in *vacuo*. The two distereoisomers were separated by preparative HPLC (linear gradient 30%-90%B in 25 min) to obtain:

Example 21 (Tab IV) (R,R,S isomer) , retention time 13 min, 30 mg

^{1}H-NMR (DMSO-d_6) δ 8.45 and 8.35 (d, 1H, NH); 7.50-6.70 (m, 14H); 5.80 and 5.45 (d, 1H), 4.00-3.15 (m, 4H), 3.05 (m, 2H), 2.50-2.00 (m, 6H), 2.00-1.10 (m 4H).

(R,R,R isomer), retention time 15 min, 35 mg

^{1}H-NMR (DMSO-d_6) δ 8.45 and 8.20 (d, 1H, NH); 7.50-6.80 (m, 14H); 5.85 and 5.45 (d, 1H), 3.80-2.80 (m, 6H), 2.50-2.00 (m, 6H), 2.00-1.10 (m 4H).

Microplate protease activity assay

[0083] The HCV-protease (J strain) was stored until use at -80°C in 250 mM NaCl, phosphate buffer pH 6.5, 50% glycerol, 0.1% CHAPS. As protease co-factor the peptide Pep4AK (KKKGSVVIVGRIILSGR-NH_2), spanning the central hydrophobic core (residues 21-34) of the NS4A protein, with a three-lysine tag at the N-terminus to increase solubility (Bianchi, E. et al., *Biochemistry* 36, 7890-7897; 1997), was used. Pep4AK was stored at -80°C in DMSO; the tritiated substrate Ac-DEMEECASHLPYK (^{3}H-Ac)-NH_2 and the corresponding cold substrate Ac-DEMEECASHLPYK(Ac)-NH_2 were stored at -80°C in DMSO/DTT.

[0084] The assay was run in Costar polypropylene 96-well plates. The composition of the reaction mixture was as follows (100 µl):

Glycerol	15%
DTT	30 mM
Hepes pH 7,5	50 mM
Triton X-100	0.05%
Protease	10 nM
hot + cold substrate	5 μM (300.000 cpm)
Pep4AK	15 μM

[0085] Test compounds were dissolved - in DMSO (final concentration 10% DMSO) Pep4AK was pre-incubated with protease for 5 min prior to addition of substrate mix. In these conditions, the substrate Km was 7±2 μM. Test compounds were added at 8 different concentrations in 8 different wells. Plates were shaken for 30 minutes at room temperature, then an ionic exchange resin (100 μl of 20% Fractogel TSK-DEAE® 650S, Merck) was added to capture unprocessed substrate and plates shaken for another 10 minutes. After allowing the resin to settle by centrifugation, 30 μl of the reaction mix were transferred in a 96-well plate (Picoplate, Packard), admixed with 250 μl of scintillation cocktail Microscint 40, and the radioactivity measured in a scintillation Packard Top Count β-counter.

[0086] IC_{50} was calculated from the test compound dilution curve, as the concentration of compound giving 50% inhibitions.

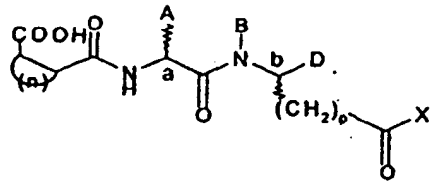
ABBREVIATIONS AND SYMBOLS USED IN THE TEXT

[0087]

ACC, acryloyl chloride;
Cha, cyclohexylalanine;
CHAPS, 3-[(3-colamidopropyl)-dimethyl-ammonium] -1-propan-sulfonate;
DCM, dichloromethane;
DIEA, diisopropylethylamine;
DMF, N,N'-dimethylformamide;
DMSO, dimethyl sulfoxide;
DTT = Ditiotreithol
EDCA, ethyl-diisopropylcarbodiimide;
Fmoc, 9-fluorenylmethyloxycarbonyl;
HATU, [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate];
HOBt, N-hydroxybenzotrlazole;
Phg, phenylglycine;
PTS, p-toluensulphonate;
PyBOP, (benzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate;
tBu, *tert*-butyl;
TEA, triethylamine;
TFA, trifluoroacetic acid.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt or ester thereof:



(I)

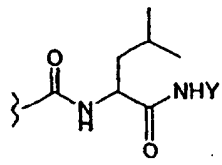
wherein:

represents a benzene ring or a non-aromatic carbocyclic ring and (n) is the total number of carbon atoms in the carbocyclic ring and is from 4 to 8;

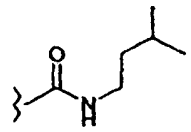
A is (i) cyclohexylmethyl- or (ii) phenyl optionally substituted with from 1 to 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, -O-C_{1-4} alkyl, O-C_{1-4} fluoroalkyl, and R^a-C(=O)O-, where R^a is naphthylmethyl-, 2,2-diphenylethyl-, or carboxycyclohexyl-;

B is hydrogen, lower alkyl of 1-6 carbon atoms or is an aralkyl group containing from 7 to 18 carbon atoms in which the aryl group is optionally substituted with one or more substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, -O-C_{1-4} alkyl, and -O-C_{1-4} fluoroalkyl;

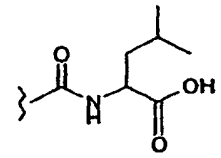
D is hydrogen, or a group of formula:



;



; or



where Y is hydrogen, an alkyl group containing 1 to 6 carbon atoms, or a cycloalkyl group containing 3 to 8 carbon atoms;

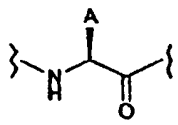
each of the stereocentres a and b is independently in the R configuration or the S configuration;

p is 1 or 2; and

X is selected from hydroxyl, and -O-C_{1-6} alkyl groups;

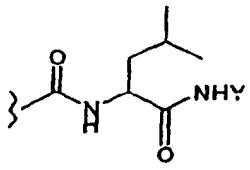
provided that if B is hydrogen or lower alkyl, D is not also hydrogen, and if D is hydrogen B is an aralkyl group.

2. A compound, salt or ester according to claim 1 wherein the stereochemistry at group A is as shown:

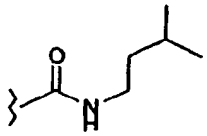


3. A compound, salt or ester according to claim 1 or claim 2 wherein B is hydrogen or a lower alkyl group and D is

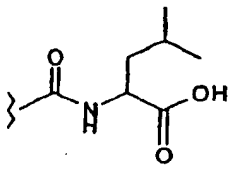
one of the substituents



;



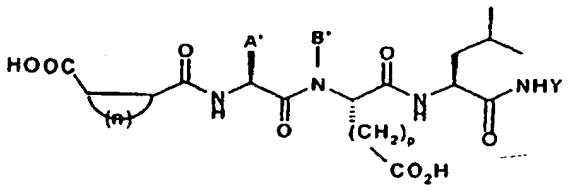
; or



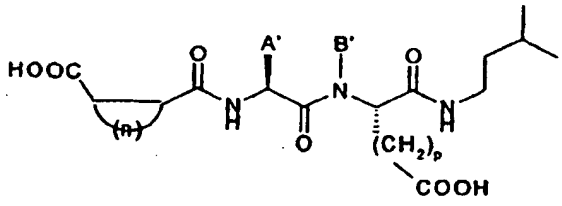
;

where Y is as defined in claim 1.

4. A compound according to claim 3 having the formula (II) or (II)', or a pharmaceutically acceptable salt or ester thereof:



(II)



(II')

wherein p, Y and

are as defined in claim 1;

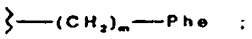
B' is hydrogen or lower alkyl; and

A' is cyclohexylmethyl-, phenyl, o-fluorophenyl or p-chlorophenyl.

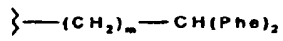
5. An enantiomer or diastereomer of a compound, salt or ester according to claim 4, or a mixture of enantiomeric and/or diastereomeric forms of said compound, salt or ester.

6. A compound, salt or ester according to claim 1 or 2 wherein D is hydrogen and B is an aralkyl group in which the aryl is optionally substituted with from 1 to 3 substituents independently selected from chloro, fluoro, methyl, CF_3, OCH_3 and OCF_3.

7. A compound, salt or ester according to claim 6 wherein the aralkyl group B is a group of formula:

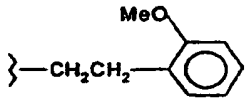


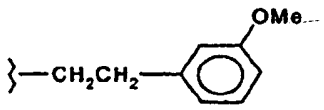
or

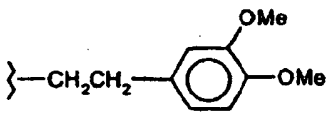


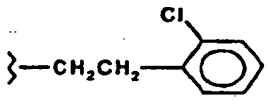
where m is 1 or 2, and Phe is phenyl optionally substituted with from 1 to 3 substituents independently selected from chloro, fluoro, methyl, CF_3, OCH_3 and OCF_3.

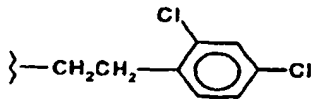
8. A compound, salt or ester according to claim 7 wherein the group B is selected from:

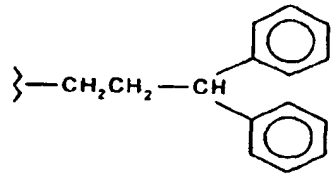


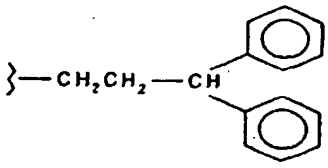




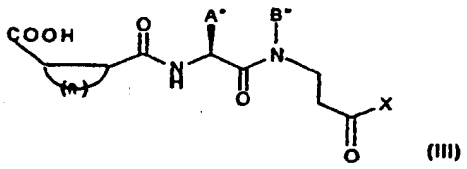








9. A compound, according to claim 7 or 8 having the formula (III), or a pharmaceutically acceptable salt or ester thereof:



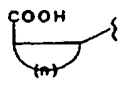
(III)

wherein

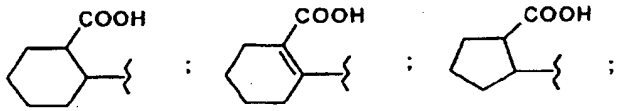
is as defined in claim 1, B" is an aralkyl group as set out in claim 6 or claim 7 and A" is cyclohexylmethyl-, phenyl, p-bromophenyl, p-trifluoromethylphenyl or o-fluorophenyl.

10. An enantiomer of the compound, salt or ester of claim 9, or a mixture of said compound, salt or ester with its enantiomer.

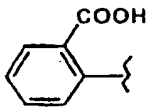
11. A compound, salt or ester according to any one of the preceding claims wherein the group



is selected from



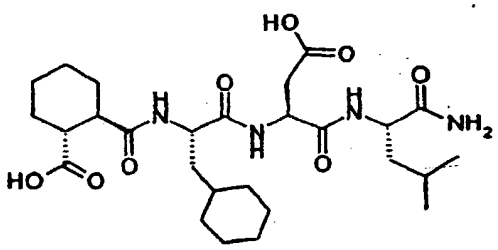
and



12. A compound, salt or ester according to claim 11 wherein the carbocyclic ring is a cyclohexyl or cyclopentyl ring whose substituents are trans to each other.

13. A compound, salt or ester according to claim 12 wherein the stereochemistry in the carbocyclic ring is 1R,2R.

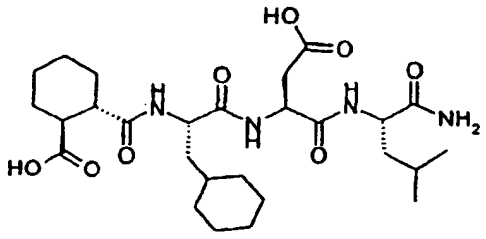
14. A compound of formula (IV), or a pharmaceutically acceptable salt or ester thereof:



(IV)

wherein the chiral centres are in the configuration R,R,S,S,S.

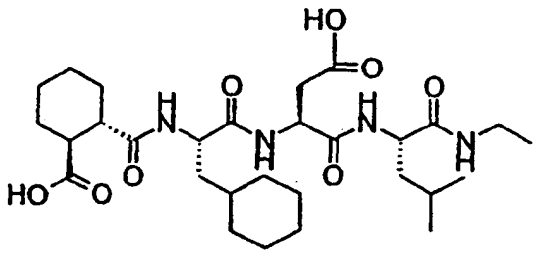
15. A compound of formula (V), or a pharmaceutically acceptable salt or ester thereof:



(V)

wherein the chiral centres are in the configuration S,S,S,S,S.

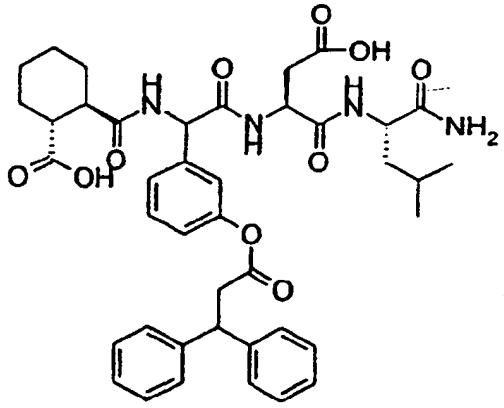
16. A compound of formula (VI), or a pharmaceutically acceptable salt or ester thereof:



(VI)

wherein the chiral centres are in the configuration R,R,S,S,S.

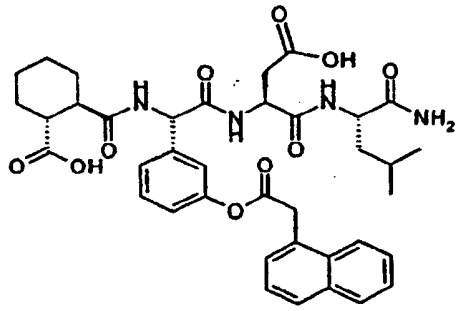
17. A compound of formula (VII), or a pharmaceutically acceptable salt or ester thereof:



(VII)

wherein the chiral centres are in the configuration R,R,[R/S],S,S.

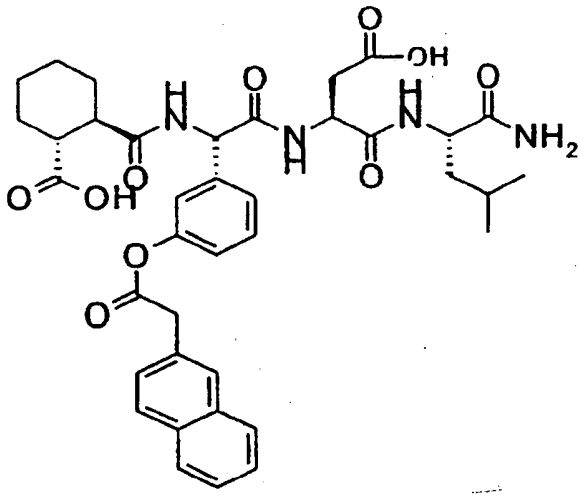
18. A compound of formula (VIII), or a pharmaceutically acceptable salt or ester thereof:



(VIII)

wherein the chiral centres are in the configuration R,R,S,S,S.

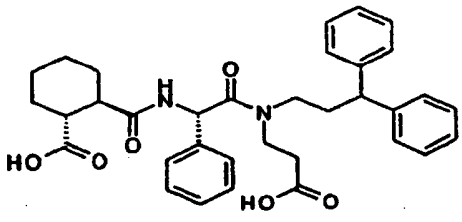
19. A compound of formula (IX), or a pharmaceutically acceptable salt or ester thereof:



(IX)

wherein the chiral centres are in the configuration R,R,S,S,S.

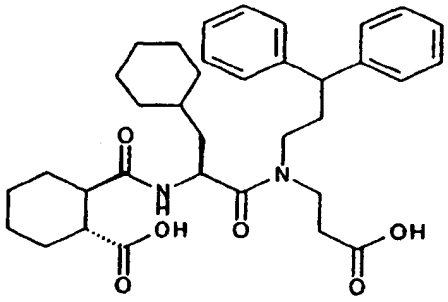
20. A compound of formula (X), or a pharmaceutically acceptable salt or ester thereof:



(X)

wherein the chiral centres are in the configuration R,R,S.

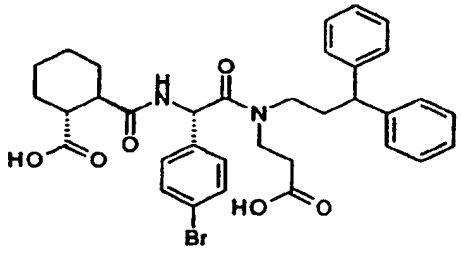
21. A compound of formula (XI), or a pharmaceutically acceptable salt or ester thereof:



(XI)

wherein the chiral centres are in the configuration R,R,S.

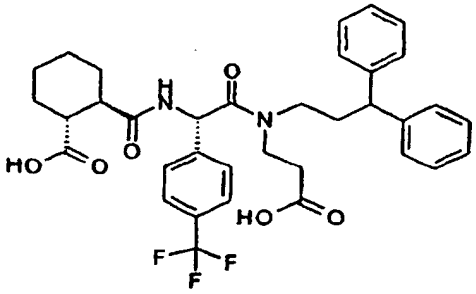
22. A compound of formula (XII), or a pharmaceutically acceptable salt or ester thereof:



(XII)

wherein the chiral centres are in the configuration R,R,S.

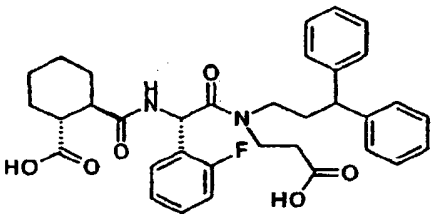
23. A compound of formula (XIII), or a pharmaceutically acceptable salt or ester thereof:



(XIII)

wherein the chiral centres are in the configuration R,R,S.

24. A compound of formula (XIV), or a pharmaceutically acceptable salt or ester thereof:



(XIV)

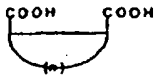
wherein the chiral centres are in the configuration R,R,S.

25. A compound, salt or ester according to any one of the preceding claims for pharmaceutical use.

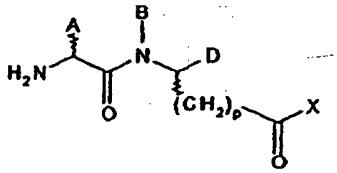
26. The use of a compound, salt or ester according to any one of claims 1 to 24 in the manufacture of a medicament for the prevention or treatment of hepatitis C virus infection, or a related condition.

27. A pharmaceutical composition comprising a compound, salt or ester of any one of claims 1 to 24 and a pharmaceutically acceptable excipient, diluent, or carrier and/or with another therapeutically or prophylactically active agent.

28. A method for the preparation of a compound according to claim 1 comprising condensing a diacid of formula:



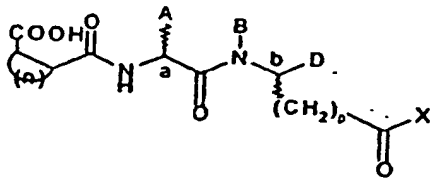
or an activated form thereof, with a suitably protected molecule of formula:



where n, A, B, D, p and X are as defined in claim 1.

Patentansprüche

1. Eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(I)

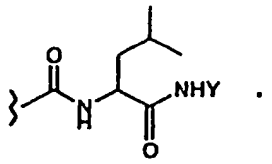
wobei:

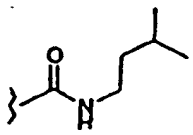
einen Benzolring oder einen nichtaromatischen carbocyclischen Ring bedeutet und (n) die Gesamtzahl an Kohlenstoffatomen in dem carbocyclischen Ring ist und 4 bis 8 beträgt,

A ist (i) Cyclohexylmethyl- oder (ii) Phenyl, gegebenenfalls substituiert mit 1 bis 3 Substituenten, unabhängig ausgewählt aus Halogen, C_{1-4}-Alkyl, C_{1-4}-Fluoralkyl, -O-C_{1-4}-Alkyl, O-C_{1-4}-Fluoralkyl und R^a-C(=O)O-, wobei R^a Naphthylmethyl-, 2,2-Diphenylethyl- oder Carboxycyclohexyl- ist,

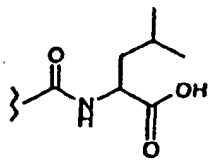
B ist Wasserstoff, Niedrigalkyl mit 1-6 Kohlenstoffatomen oder eine Aralkylgruppe mit 7 bis 18 Kohlenstoffatomen, wobei die Arylgruppe gegebenenfalls mit einem oder mehreren Substituenten, unabhängig ausgewählt aus Halogen, C_{1-4}-Alkyl, C_{1-4}-Fluoralkyl, -O-C_{1-4}-Alkyl und -O-C_{1-4}-Fluoralkyl, substituiert ist,

D Wasserstoff oder eine Gruppe der Formel:





oder

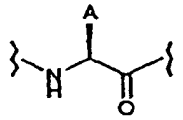


ist,

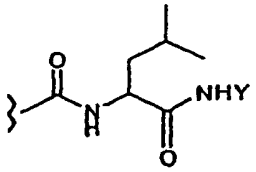
wobei Y Wasserstoff, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder eine Cycloalkylgruppe mit 3 bis 8 Kohlenstoffatomen ist,

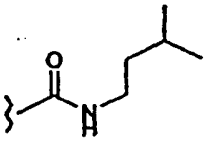
jedes der Stereozentren a und b unabhängig die R-Konfiguration oder die S-Konfiguration besitzt,
p 1 oder 2 ist und
X ausgewählt ist aus Hydroxyl und -O-C_{1-6}-Alkylgruppen,
mit der Maßgabe, daß, wenn B Wasserstoff oder Niedrigalkyl ist, D nicht ebenfalls Wasserstoff ist, und, wenn D Wasserstoff ist, B eine Aralkylgruppe ist.

2. Eine Verbindung, ein Salz oder ein Ester gemäß Anspruch 1, wobei die Stereochemie in Gruppe A wie gezeigt ist:

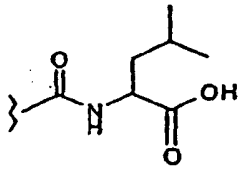


3. Eine Verbindung, ein Salz oder ein Ester gemäß Anspruch 1 oder Anspruch 2, wobei B Wasserstoff oder eine Niedrigalkylgruppe ist und D einer der Substituenten



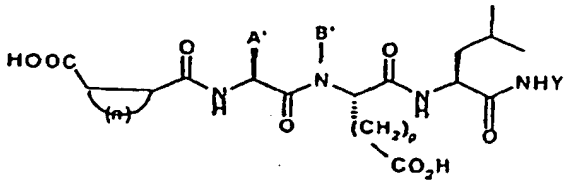


oder

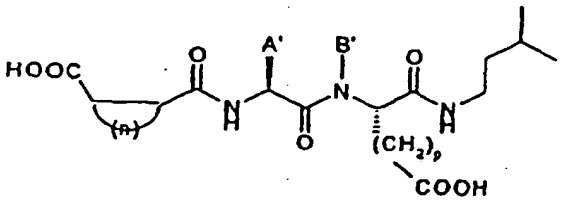


ist,
wobei Y wie in Anspruch 1 definiert ist.

4. Eine Verbindung gemäß Anspruch 3 mit der Formel (II) oder (II)' oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(II)



(II')

wobei p, Y und

wie in Anspruch 1 definiert sind,

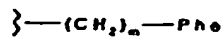
B' Wasserstoff oder Niedrigalkyl ist und

A' Cyclohexylmethyl-, Phenyl, o-Fluorphenyl oder p-Chlorphenyl ist.

5. Ein Enantiomer oder Diastereomer einer Verbindung, eines Salzes oder eines Esters gemäß Anspruch 4 oder eine Mischung aus enantiomeren und/oder diastereomeren Formen der Verbindung, des Salzes oder des Esters.

6. Eine Verbindung, ein Salz oder ein Ester gemäß Anspruch 1 oder 2, wobei D Wasserstoff ist und B eine Aralkylgruppe ist, bei der das Aryl gegebenenfalls mit 1 bis 3 Substituenten, unabhängig ausgewählt aus Chlor, Fluor, Methyl, CF_3, OCH_3 und OCF_3, substituiert ist.

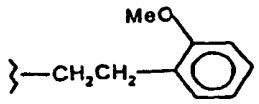
7. Eine Verbindung, ein Salz oder ein Ester gemäß Anspruch 6, wobei die Aralkylgruppe B eine Gruppe der Formel:

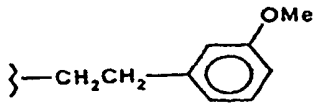


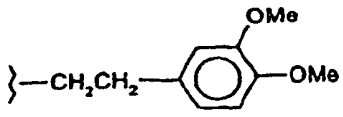
oder

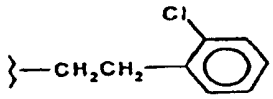
ist, wobei m 1 oder 2 ist und Phe Phenyl ist, gegebenenfalls substituiert mit 1 bis 3 Substituenten, unabhängig ausgewählt aus Chlor, Fluor, Methyl, CF_3, OCH_3 und OCF_3.

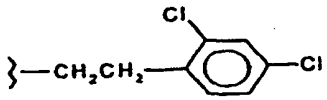
8. Eine Verbindung, ein Salz oder ein Ester gemäß Anspruch 7, wobei die Gruppe B ausgewählt ist aus:

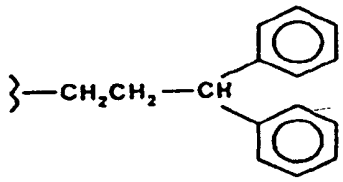


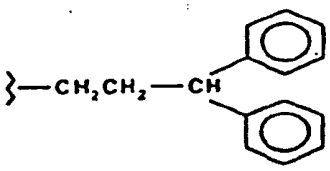




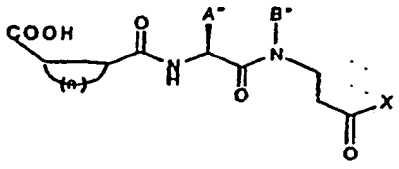








9. Eine Verbindung gemäß Anspruch 7 oder 8 mit der Formel (III) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(III)

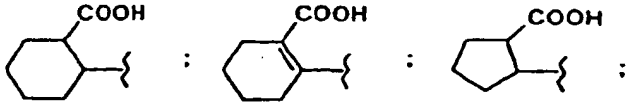
wobei

wie in Anspruch 1 definiert ist, B" eine Aralkylgruppe ist, wie sie in Anspruch 6 oder Anspruch 7 definiert ist, und A" Cyclohexylmethyl-, Phenyl, p-Bromphenyl, p-Trifluormethylphenyl oder o-Fluorphenyl ist.

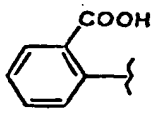
10. Ein Enantiomer der Verbindung, des Salzes oder des Esters nach Anspruch 9 oder eine Mischung der Verbindung, des Salzes oder des Esters mit ihrem/seinem Enantiomer.

11. Eine Verbindung, ein Salz oder ein Ester gemäß irgendeinem der vorhergehenden Ansprüche, wobei die Gruppe

ausgewählt ist aus



und

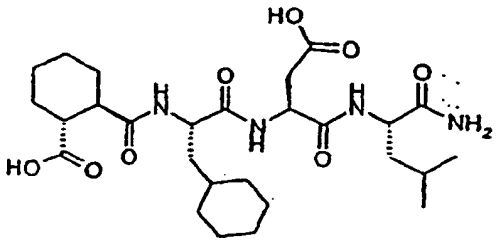


.

12. Eine Verbindung, ein Salz oder ein Ester gemäß Anspruch 11, wobei der carbocyclische Ring ein Cyclohexyl- oder Cyclopentylring ist, dessen Substituenten trans zueinander stehen.

13. Eine Verbindung, ein Salz oder ein Ester gemäß Anspruch 12, wobei die Stereochemie in dem carbocyclischen Ring 1R,2R ist.

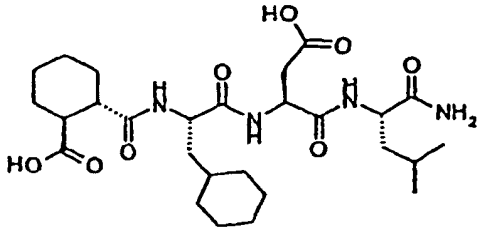
14. Eine Verbindung der Formel (IV) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(IV),

wobei die Chiralitätszentren in der Konfiguration R,R,S,S,S vorliegen.

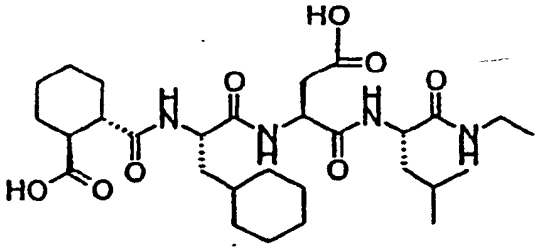
15. Eine Verbindung der Formel (V) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(V),

wobei die Chiralitätszentren in der Konfiguration S,S,S,S,S vorliegen.

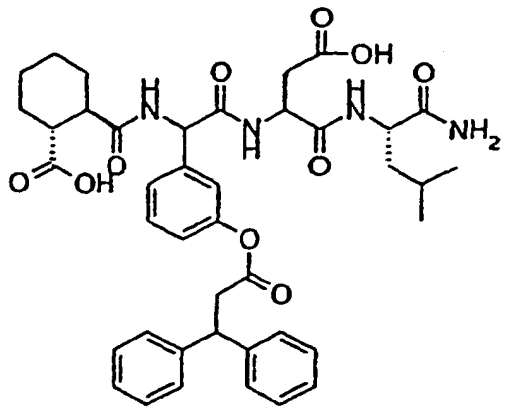
16. Eine Verbindung der Formel (VI) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(VI),

wobei die Chiralitätszentren in der Konfiguration R,R,S,S,S vorliegen.

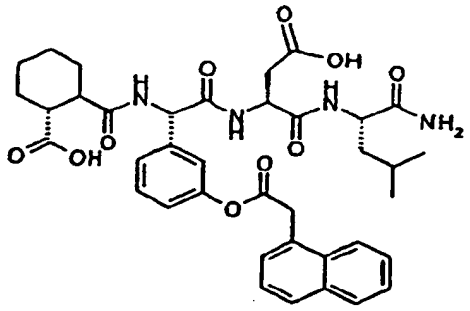
17. Eine Verbindung der Formel (VII) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(VII) ,

wobei die Chiralitätszentren in der Konfiguration R,R,[R/S],S,S vorliegen.

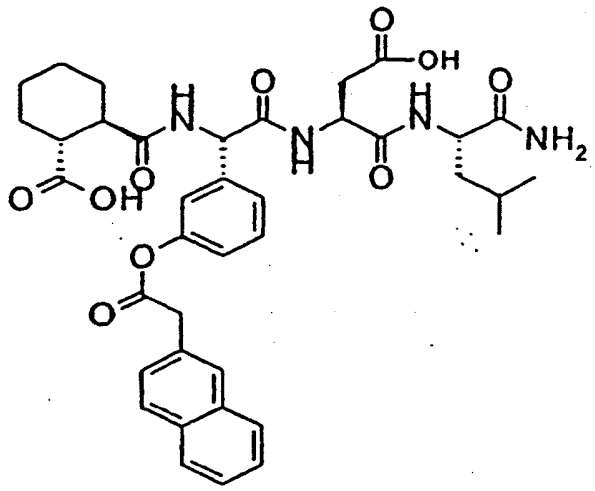
18. Eine Verbindung der Formel (VIII) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(VIII) ,

wobei die Chiralitätszentren in der Konfiguration R,R,S,S,S vorliegen.

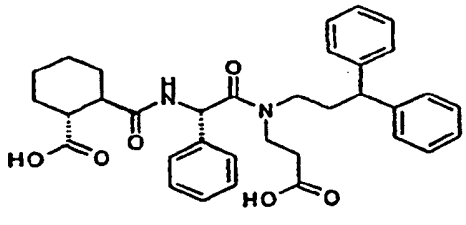
19. Eine Verbindung der Formel (IX) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(IX) ,

wobei die Chiralitätszentren in der Konfiguration R,R,S,S,S vorliegen.

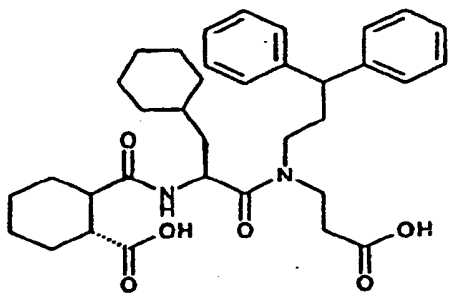
20. Eine Verbindung der Formel (X) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(X) ,

wobei die Chiralitätszentren in der Konfiguration R,R,S vorliegen.

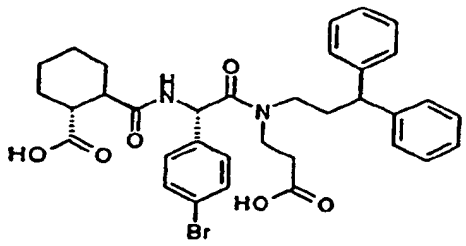
21. Eine Verbindung der Formel (XI) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(XI) ,

wobei die Chiralitätszentren in der Konfiguration R,R,S vorliegen.

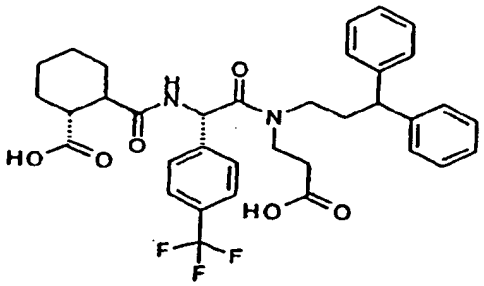
22. Eine Verbindung der Formel (XII) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(XII),

wobei die Chiralitätszentren in der Konfiguration R,R,S vorliegen.

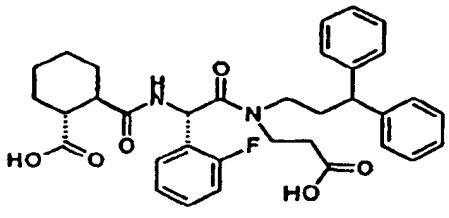
23. Eine Verbindung der Formel (XIII) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(XIII),

wobei die Chiralitätszentren in der Konfiguration R,R,S vorliegen.

24. Eine Verbindung der Formel (XIV) oder ein pharmazeutisch annehmbares Salz oder ein pharmazeutisch annehmbarer Ester davon:



(XIV),

wobei die Chiralitätszentren in der Konfiguration R,R,S vorliegen.

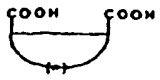
25. Eine Verbindung, ein Salz oder ein Ester gemäß irgendeinem der vorhergehenden Ansprüche zur pharmazeutischen Verwendung.

26. Die Verwendung einer Verbindung, eines Salzes oder eines Esters gemäß irgendeinem der Ansprüche 1 bis 24

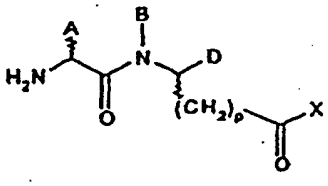
zur Herstellung eines Medikaments zur Prävention oder Behandlung einer Hepatitis-C-Virusinfektion oder eines verwandten Zustands.

27. Eine pharmazeutische Zusammensetzung, die eine Verbindung, ein Salz oder einen Ester nach irgendeinem der Ansprüche 1 bis 24 und einen pharmazeutisch annehmbaren Hilfsstoff, ein pharmazeutisch annehmbares Verdünnungsmittel oder einen pharmazeutisch annehmbaren Träger und/oder ein weiteres therapeutisch oder prophylaktisch wirksames Mittel enthält.

28. Ein Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, umfassend die Kondensation einer Disäure der Formel:



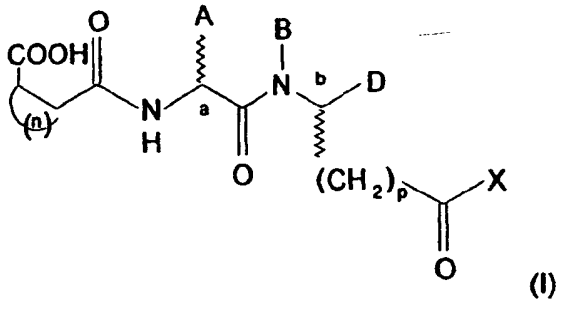
oder einer aktivierten Form davon mit einem geeignet geschützten Molekül der Formel:



wobei n, A, B, D, p und X wie in Anspruch 1 definiert sind.

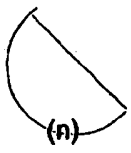
Revendications

1. Composé de formule (I), ou un sel ou ester pharmaceutiquement acceptable correspondant;



(I)

dans laquelle

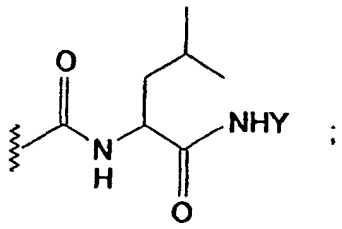


représente un cycle benzénique ou un cycle carbocyclique non aromatique et (n) désigne le nombre total d'atomes de carbone dans le cycle carbocyclique et varie de 4 à 8 ;

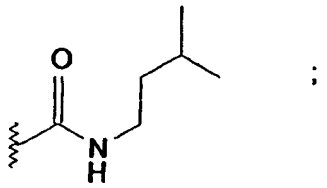
A est un groupe (i) cyclohexylméthyl- ou (ii) phényle éventuellement substitué par 1 à 3 substituants indépendamment choisis parmi un groupe halogène, alkyle en C_1 à C_4, fluoroalkyle en C_1 à C_4, -O-alkyle en C_1 à C_4, O-fluoroalkyle en C_1 à C_4, et R^a-C(=O)O-, où Ra est un groupe naphtylméthyl-, 2, 2-diphényléthyl-, ou carboxy-cyclohexyl-;

B est un atome d'hydrogène, un groupe alkyle inférieur de 1 à 6 atomes de carbone ou est un groupe aralkyle contenant de 7 à 18 atomes de carbone, dans lequel le groupe aryle est éventuellement substitué par un ou plusieurs substituants indépendamment choisis parmi un groupe halogène, alkyle en C_1 à C_4, fluoroalkyle en C_1 à C_4, -O-alkyle en C_1 à C_4, et -O-fluoroalkyle en C_1 à C_4;

D est un atome d'hydrogène, ou un groupe de formule :

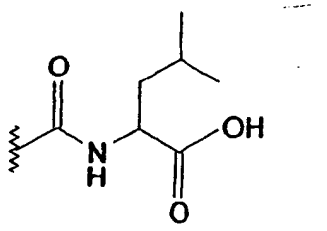


;



;

ou



où Y est un atome d'hydrogène, un groupe alkyle contenant de 1 à 6 atomes de carbone, ou un groupe cycloalkyle contenant de 3 à 8 atomes de carbone ;

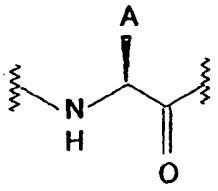
chacun des centres chiraux a et b est indépendamment de configuration R ou de configuration S ;

p vaut 1 ou 2 ; et

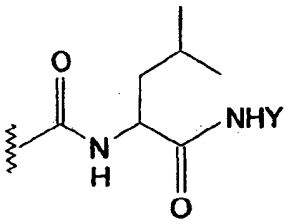
X est choisi parmi les groupes hydroxyle, et —O-alkyle en C_1 à C_6

à la condition que si B est un atome d'hydrogène ou un groupe alkyle inférieur, D ne soit pas un atome d'hydrogène, et que si D est un atome d'hydrogène, B soit un groupe aralkyle.

2. Composé, sel ou ester selon la revendication 1, dans lequel la configuration stéréochimique du groupe A est comme indiqué ici :



3. Composé, sel ou ester selon la revendication 1 ou la revendication 2, dans lequel B est un atome d'hydrogène ou un groupe alkyle inférieur et D est l'un des substituants



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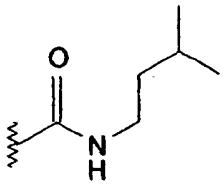
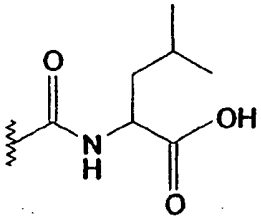
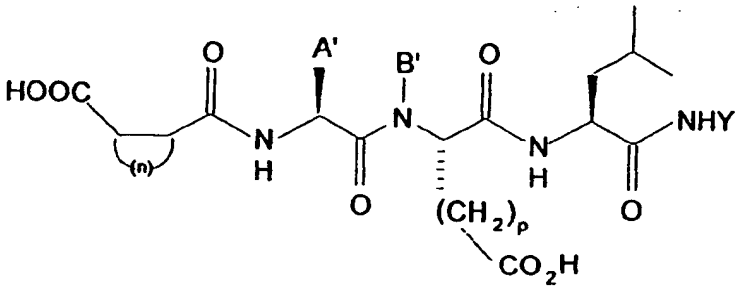


ou

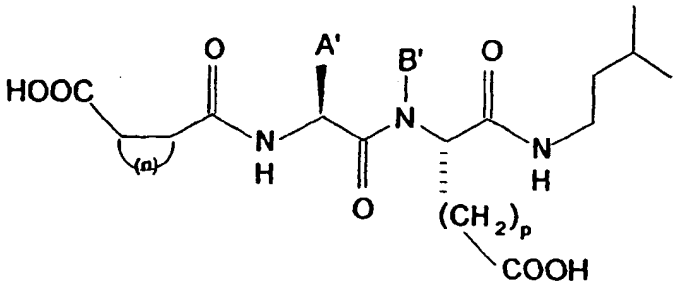


où Y est tel que défini à la revendication 1.

4. Composé selon la revendication 3, ayant la formule (II) ou (II)', ou un sel ou ester pharmaceutiquement acceptable correspondant :



(II)



(II')

dans lesquelles p, Y et

sont tels que définis dans la revendication 1 ;

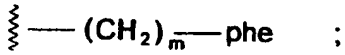
B' est un atome d'hydrogène ou un alkyle inférieur; et

A' est un groupe cyclohexylméthyle, phényle, o-fluorophényle ou p-chlorophényle.

5. Enantiomère ou diastéréomère d'un composé, sel ou ester selon la revendication 4, ou un mélange de formes énantiomériques et/ou diastéréomériques dudit composé, sel ou ester.

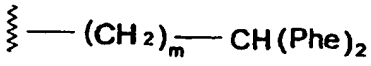
6. Composé, sel ou ester selon la revendication 1 ou 2, dans lequel D est un atome d'hydrogène et B est un groupe aralkyle dans lequel le groupe aryle est éventuellement substitué par 1 à 3 substituants indépendamment choisis parmi le groupe chloro, fluoro, méthyle, CF_3, OCH_3 et OCF_3.

7. Composé, sel ou ester selon la revendication 6, dans lequel le groupe aralkyle B est un groupe de formule :



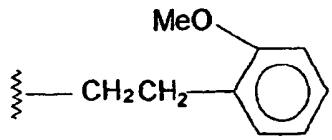
;

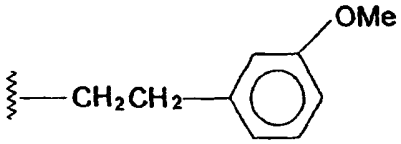
ou

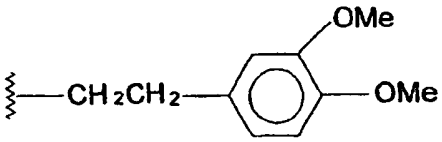


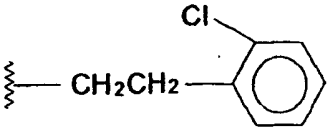
où m vaut 1 ou 2, et Phe est un groupe phényle éventuellement substitué par 1 à 3 substituants indépendamment choisis parmi le groupe chloro, fluoro, méthyle, CF_3, OCH_3 et OCF_3.

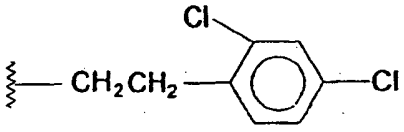
8. Composé, sel ou ester selon la revendication 7, dans lequel le groupe B est choisi parmi :

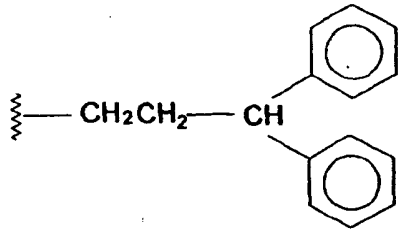


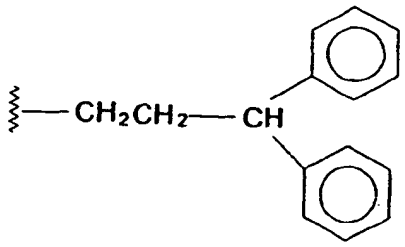




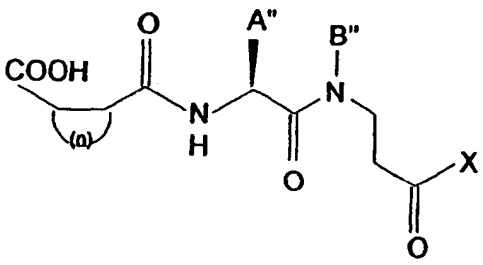








9. Composé selon la revendication 7 ou 8 ayant la formule (III), ou un sel ou ester pharmaceutiquement acceptable correspondant :



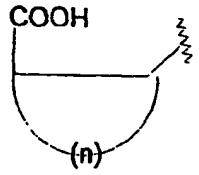
(III)

dans laquelle

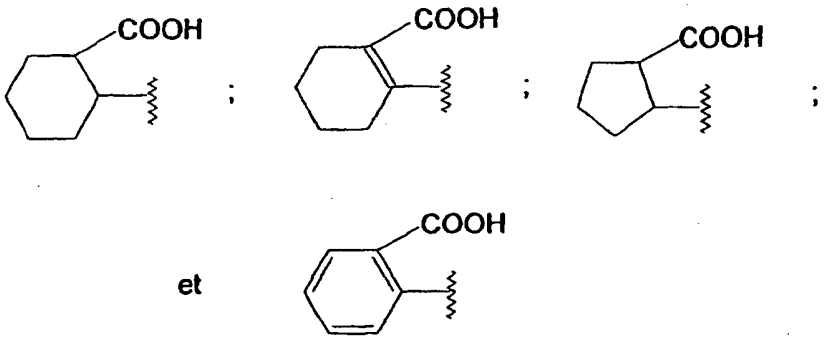
est tel que défini dans la revendication 1, B" est un groupe aralkyle comme défini dans la revendication 6 ou la revendication 7 et A" est un groupe cyclohexylméthyle, phényle, p-bromophényle, p-trifluorométhylphényle ou o-fluorophényle.

10. Enantiomère du composé, sel ou ester selon la revendication 9, ou un mélange dudit composé, sel ou ester avec l'énantiomère correspondant.

11. Composé, sel ou ester selon l'une quelconque des revendications précédentes, dans lequel le groupe



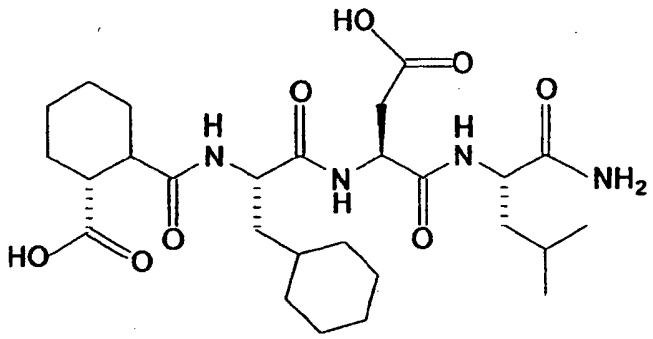
est choisi parmi



12. Composé, sel ou ester selon la revendication 11, dans lequel le noyau carbocyclique est un groupe cyclohexyle ou un noyau cyclopentyle dont les substituants sont de conformation trans l'un par rapport à l'autre.

13. Composé, sel ou ester selon la revendication 12, dans lequel la configuration stéréochimique du cycle carbocyclique est 1R, 2R.

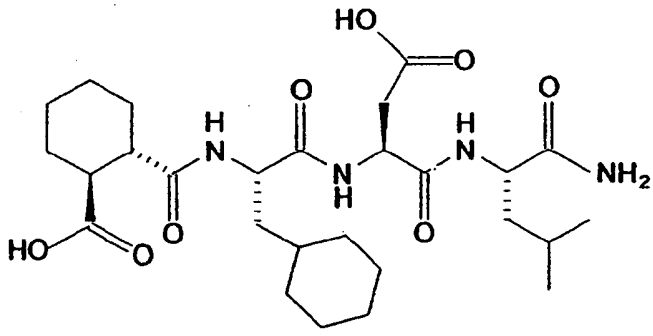
14. Composé de formule (IV), ou un sel ou ester pharmaceutiquement acceptable correspondant :



(IV)

dans laquelle les centres chiraux sont de configuration R, R, S, S, S.

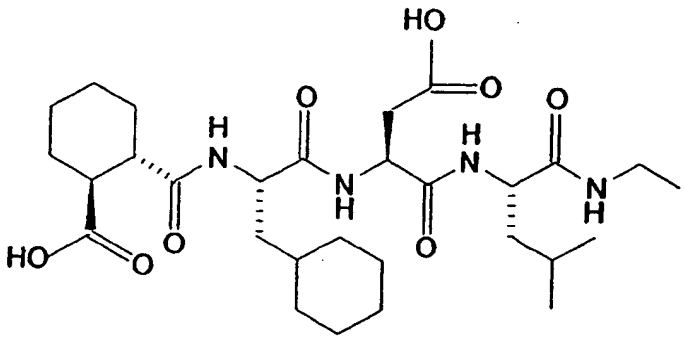
15. Composé de formule (V) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(V)

dans laquelle les centres chiraux sont de configuration S, S, S, S, S.

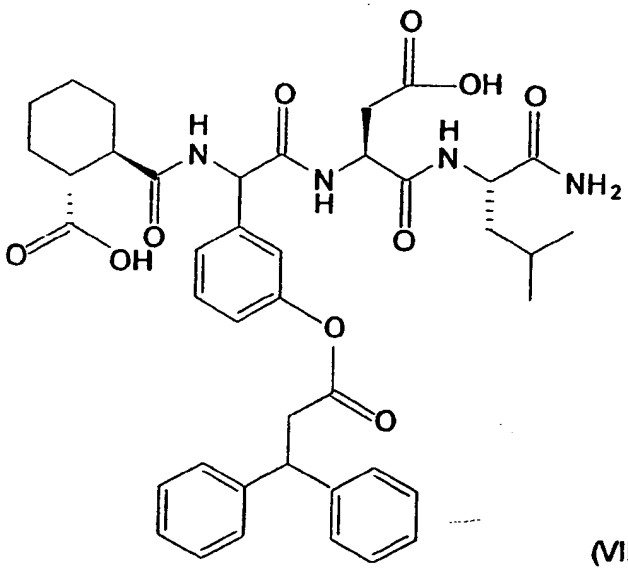
16. Composé de formule (VI) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(VI)

dans laquelle les centres chiraux sont de configuration R, R, S, S, S.

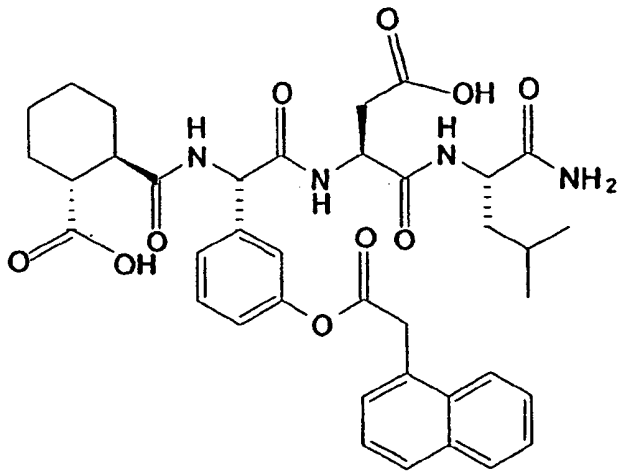
17. Composé de formule (VII) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(VII)

dans laquelle les centres chiraux sont de configuration R, R, [R/S], S, S.

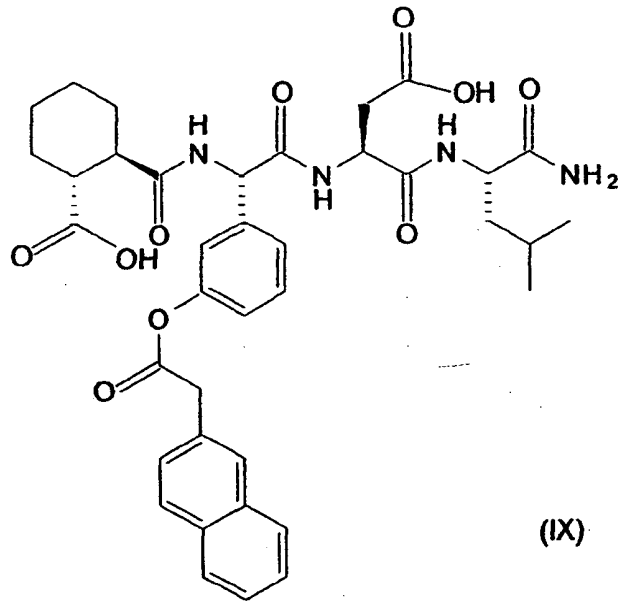
18. Composé de formule (VIII), ou un sel ou ester pharmaceutiquement acceptable correspondant :



(VIII)

dans laquelle les centres chiraux sont de configuration R, R, S, S, S.

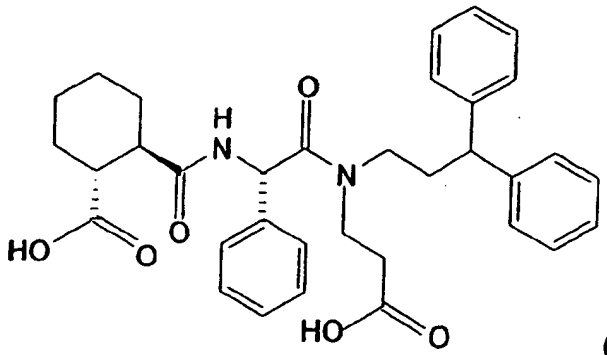
19. Composé de formule (IX) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(IX)

dans laquelle les centres chiraux sont de configuration R, R, S, S, S.

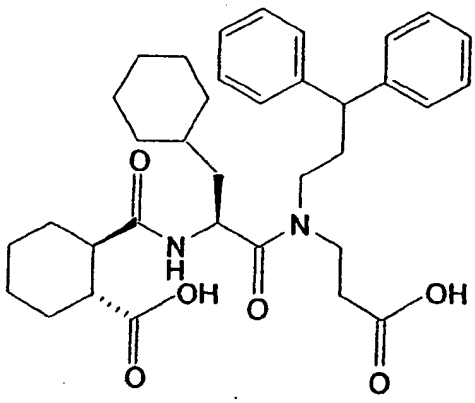
20. Composé de formule (X) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(X)

dans laquelle les centres chiraux sont de configuration R, R, S.

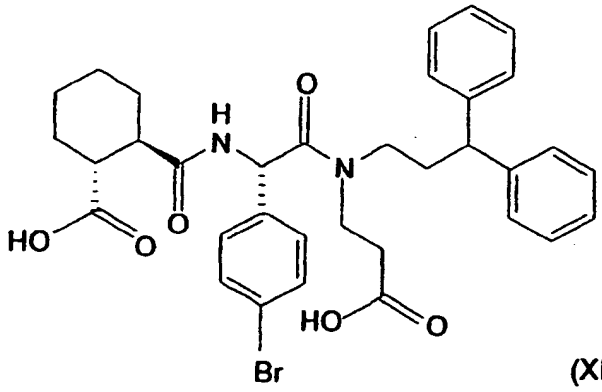
21. Composé de formule (XI) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(XI)

dans laquelle les centres chiraux sont de configuration R, R, S.

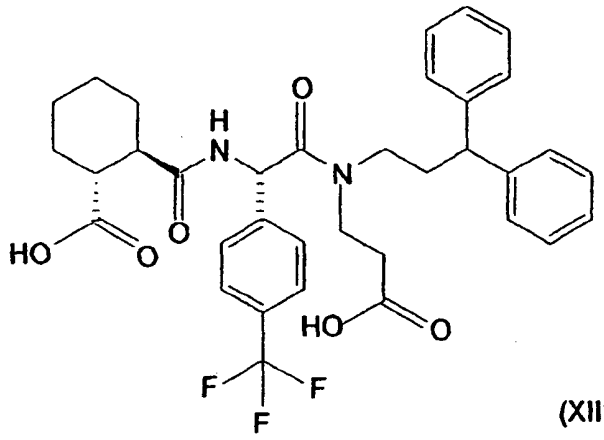
22. Composé de formule (XII) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(XII)

dans laquelle les centres chiraux sont de configuration R, R, S.

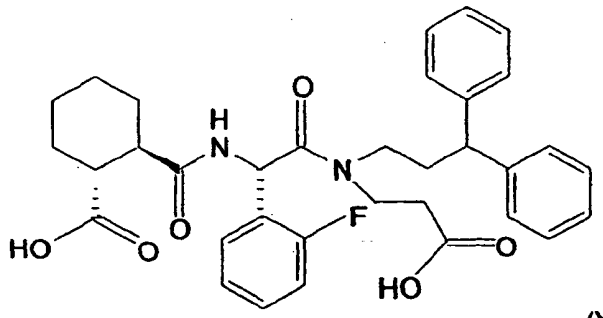
23. Composé de formule (XIII) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(XIII)

dans laquelle les centres chiraux sont de configuration R, R, S.

24. Composé de formule (XIV) ou un sel ou ester pharmaceutiquement acceptable correspondant :



(XIV)

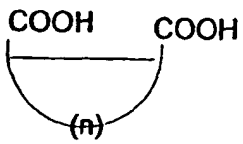
dans laquelle les centres chiraux sont de configuration R, R, S.

25. Composé, sel ou ester selon l'une quelconque des revendications précédentes à usage pharmaceutique.

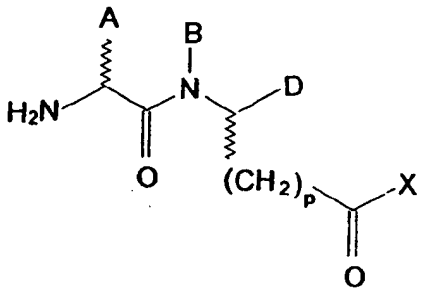
26. Utilisation d'un composé, sel ou ester selon l'une quelconque des revendications 1 à 24 pour la fabrication d'un médicament destiné à la prévention ou au traitement d'une infection par le virus de l'hépatite C, ou d'une affection apparentée.

27. Composition pharmaceutique comprenant un composé, sel ou ester selon l'une quelconque des revendications 1 à 24 et un excipient, diluant ou véhicule pharmaceutiquement acceptable et/ou un autre agent doué d'acüvité thérapeutique ou prophylactique.

28. Procédé pour la préparation d'un composé selon la revendication 1, comprenant la condensation d'un diacide de formule :



ou d'une forme activée de celui-ci, avec une molécule convenablement protégée de formule :



où n, A, B, D, p et X sont tels que définis dans la revendication 1.